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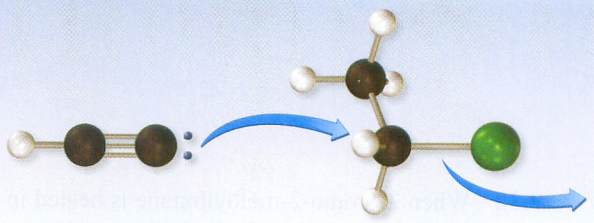

Synthetic Uses of Substitution and Elimination Reactions

INTERCONVERTING FUNCTIONAL GROUPS

CHAPTER 10

THE PREVIOUS two chapters examined the mechanisms of substitution and elimination reactions in considerable detail. The purpose of this chapter is to see how to use these reactions to make other organic compounds, our first exploration into the area of organic synthesis. In this chapter the reactions are organized according to the type of compound that is produced. First, substitution reactions are covered, reactions that can be used to convert alkyl halides and alcohols into a host of other compounds, including ethers, esters, amines, and alkanes, by using different nucleophiles. In addition, two carbon nucleophiles are introduced. The use of carbon nucleophiles in substitution reactions results in the formation of carbon–carbon bonds, a very important part of the synthesis of organic compounds. For each of these substitution reactions, the factors that affect the yield are discussed, along with any limitations the reaction might have. Then the use of elimination reactions to prepare compounds containing double and triple bonds is presented, along with a discussion of the limitations of these reactions.

The number of reactions in this chapter may seem overwhelming at first. The key to success is to remember that nucleophiles react with electrophiles. If you can identify the nucleophile or base and the electrophilic carbon (the one bonded to the leaving group) in each reaction and recall the factors that affect the competition between the two substitution mechanisms and the two elimination mechanisms, the material you have to learn will be much more manageable.

MASTERING ORGANIC CHEMISTRY

- Predicting the Major Products of Substitution and Elimination Reactions
- Predicting the Stereochemistry of Substitution and Elimination Reactions
- Writing the Mechanisms for Substitution and Elimination Reactions
- Using Substitution and Elimination Reactions to Synthesize Compounds

10.1 SUBSTITUTION REACTIONS

In general, reactions proceeding by the S_N2 mechanism are more commonly employed for syntheses than are reactions proceeding by the S_N1 mechanism because of potential

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complications, such as loss of stereochemistry or rearrangement, that often accompany reactions involving carbocations. The major factor that decreases the yields of S_N2 reactions is competing elimination reactions. Elimination can often be decreased by minimizing steric hindrance at the reaction site and decreasing the basicity of the nucleophile.

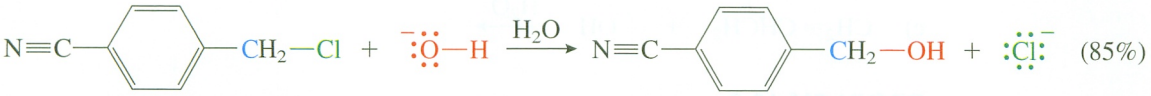
Compounds in which the leaving group is attached to a methyl or primary carbon usually give excellent yields in S_N2 substitutions. If the leaving group is attached to a secondary carbon, yields are still acceptable for nucleophiles that are only weakly basic. However, nucleophiles that are stronger bases often cause unacceptable amounts of elimination with secondary substrates. In such cases it is necessary to prepare the desired compound by an S_N1 pathway, if possible, or by an indirect route involving more than one step. When the leaving group is attached to a tertiary carbon, the S_N2 mechanism cannot occur. In such situations the substitution must be S_N1, and some elimination must be tolerated.

With these caveats in mind, let's see how to use these substitution reactions to prepare a variety of functional groups.

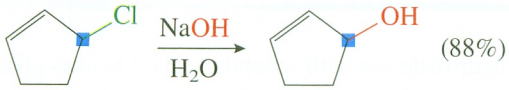
10.2 PREPARATION OF ALCOHOLS

Alcohols are widely available from a number of reactions that are described in subsequent chapters. For this reason they are often the starting materials for the preparation of other functional groups using substitution reactions. However, they can be prepared from alkyl halides, when necessary, by using either water or hydroxide ion as the nucleophile. A general equation for the reaction using hydroxide ion as the nucleophile is

Hydroxide ion, the conjugate base of water, is a strong base and a strong nucleophile and reacts by the S_N2 mechanism. As illustrated in the following example, hydroxide ion gives good yields of alcohols with primary alkyl halides:

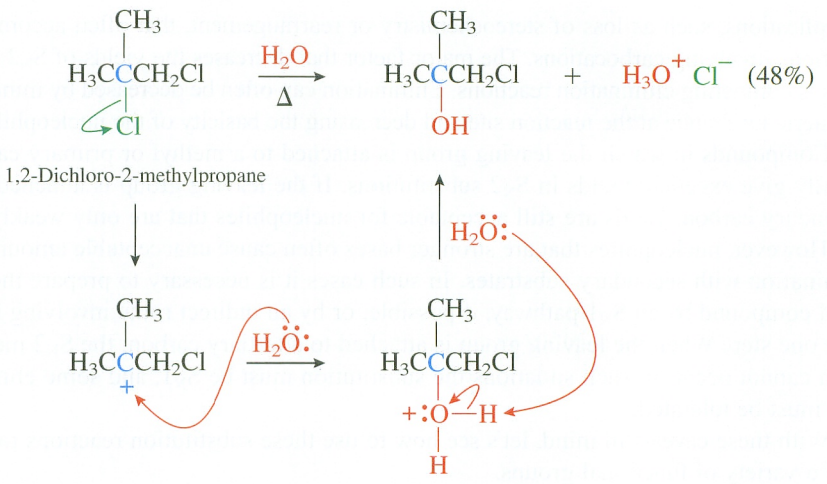


Yields are also acceptable for reactions of hydroxide ion with secondary alkyl halides if the compound is especially favorable for S_N2 reactions (halides that are allylic, benzylic, or adjacent to a carbonyl group), as shown in the following example:



Hydroxide ion is seldom used as a nucleophile with unactivated secondary halides and never with tertiary halides because of competing E2 elimination reactions. For such compounds, replacement of the halide with OH can be accomplished by using water as a nucleophile and S_N1 conditions:

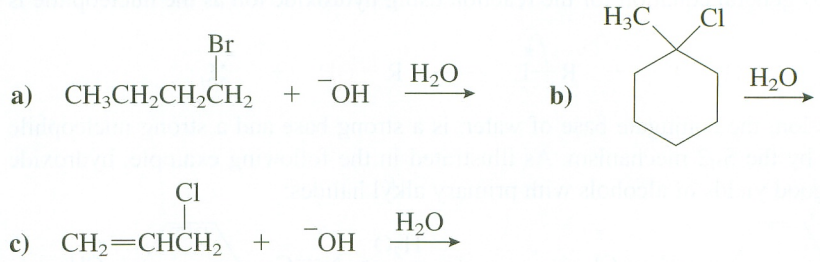
As shown in the following equation, the alkyl halide is heated in water as the solvent. (A Δ over or under a reaction arrow is used to indicate the application of heat.)



The mechanism (S_N1) for this reaction is also shown. Note that the nucleophile is water, not hydroxide ion. The second proton on the oxygen is not lost until after the oxygen has bonded to the carbon. A reaction such as this one, in which the nucleophile is also the solvent, is called a **solvolysis reaction.** In this specific case, where water is both the nucleophile and solvent, it is a **hydrolysis reaction.**

PROBLEM 10.1

Show the products of these reactions:



PROBLEM 10.2

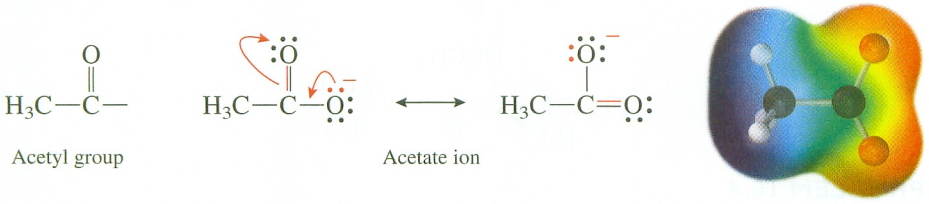
Explain why only one of the two chlorines of 1,2-dichloro-2-methylpropane is replaced by a hydroxy group when the compound is heated in water (see the preceding hydrolysis reaction).

The reaction of hydroxide ion with secondary alkyl halides gives poor yields of the substitution product because hydroxide ion, a strong base, causes too much elimination. It is not unusual in organic chemistry for a reagent to give a poor yield of the desired product in a reaction because it is too reactive. The organic chemist's solution to such a problem is to modify the reactivity of the reagent—that is, to make it less reactive so that the yield in the desired reaction is higher. This is often accomplished by attaching a group to the reagent that decreases its reactivity. This modified reagent is then used in the desired reaction. Finally, the modifying group is removed from the reagent.

This technique can be used to prepare alcohols in better yields using substitution reactions. The hydrogen of hydroxide ion is replaced with a group that makes the oxygen less basic. Decreasing the basicity of the nucleophile slows the elimination reaction

more than it slows the substitution reaction, resulting in a higher proportion of substitution in the product mixture (see Section 9.7). After the substitution is accomplished, the group that was used to replace the hydrogen must be removed so that the overall transformation is the replacement of the halide with OH.

A group that can be used to replace the hydrogen and decrease the basicity of the oxygen is the acetyl group. Thus, acetate anion is used as the nucleophile rather than hydroxide ion.



Acetate ion is a weaker base than hydroxide ion because of its resonance stabilization. For this reason, acetate ion gives higher yields of substitution products when used as a nucleophile in S_N2 reactions with secondary substrates. The resulting acetate ester can be converted to the desired alcohol in good yield by reaction with base and water. This step is not an S_N2 substitution. Instead, it begins with hydroxide ion, a nucleophile, attacking at the carbon of the carbonyl group, which is an electrophile. Ultimately, the single bond between the carbonyl carbon and the oxygen is broken. (The details of the mechanism for this reaction, called ester hydrolysis, are covered in Chapter 19.) Because the ester hydrolysis does not involve the carbon–oxygen bond that is formed in the initial S_N2 step, elimination is not a problem and the stereochemistry of that carbon–oxygen bond remains unchanged. An example of this process is shown in Figure 10.1.

In the process illustrated in Figure 10.1, acetate ion is termed a **synthetic equivalent** of hydroxide ion because the final product is the same as if hydroxide ion were used directly. But the two-step process results in a higher yield of 2-butanol than could be obtained by a direct substitution reaction of 2-bromobutane with hydroxide ion. The use of a carbonyl group to decrease the basicity or nucleophilicity of a reagent in order to

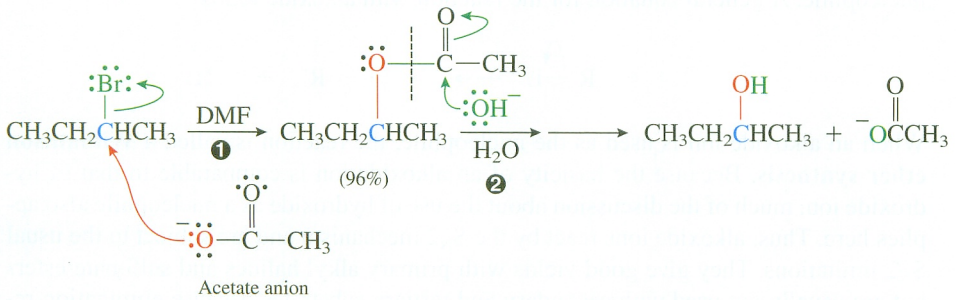


Figure 10.1

PREPARATION OF AN ALCOHOL BY THE USE OF ACETATE ION AS THE NUCLEOPHILE.

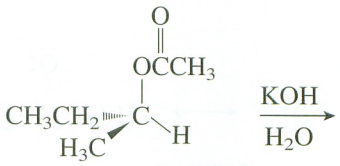
❶ Acetate ion gives good yields in S_N2 reactions at secondary carbons, especially when an aprotic solvent, such as dimethylformamide, is used.

❷ The second step is not an S_N2 reaction. Instead, the green bond between the oxygen and the carbonyl carbon is cleaved by a different mechanism. (The details of this mechanism are discussed in Chapter 19 and need not concern us here. However, to help you remember what happens, note that this process begins with the hydroxide ion nucleophile attacking the carbonyl carbon, which is an electrophile.) The red CO bond is not cleaved, so its stereochemistry does not change in this step, nor does elimination occur under these conditions. The net effect of this two-step procedure is to substitute an OH group for the Br.

provide better control of the reaction and a higher yield is a common strategy in organic synthesis.

PROBLEM 10.3

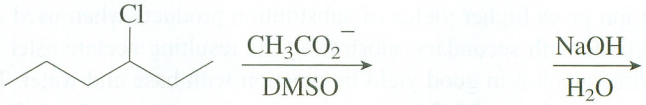
On the basis of the bond cleavage shown for this reaction in Figure 10.1, predict the stereochemistry of the product. Explain.



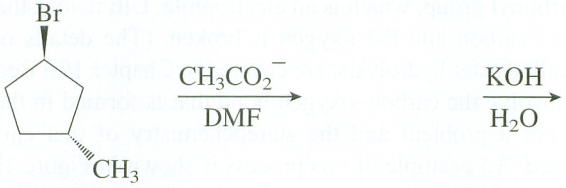
PROBLEM 10.4

Show the products of these reactions:

a)



b)



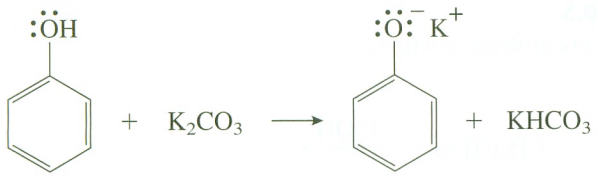
10.3 PREPARATION OF ETHERS

Ethers can be prepared by using an alcohol or its conjugate base, an alkoxide ion, as the nucleophile. A general equation for the reaction with alkoxide ion is

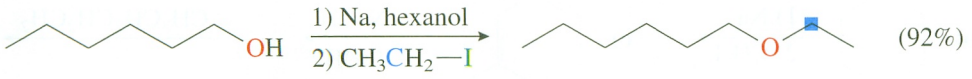
When an alkoxide ion is used as the nucleophile, the reaction is called a **Williamson ether synthesis.** Because the basicity of an alkoxide ion is comparable to that of hydroxide ion, much of the discussion about the use of hydroxide as a nucleophile also applies here. Thus, alkoxide ions react by the S_N2 mechanism and are subject to the usual S_N2 limitations. They give good yields with primary alkyl halides and sulfonate esters but are usually not used with secondary and tertiary substrates because elimination reactions predominate.

The alkoxide ion nucleophile is often prepared from the alcohol by reaction with sodium metal, as shown in the following equation for the formation of ethoxide ion from ethanol:

Because phenols are stronger acids than alcohols, nucleophilic phenoxide ions can be prepared by reacting the phenol with bases such as hydroxide ion or carbonate ion.

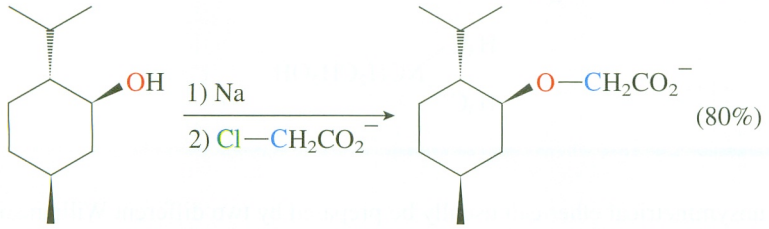


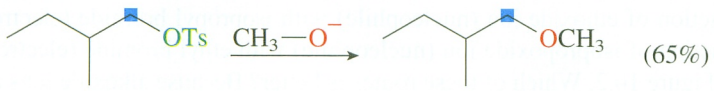
Several examples of the Williamson ether synthesis are given in the following equations:

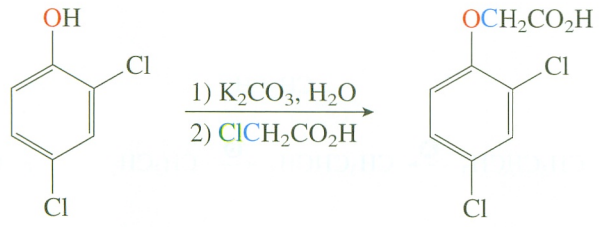


Important Convention

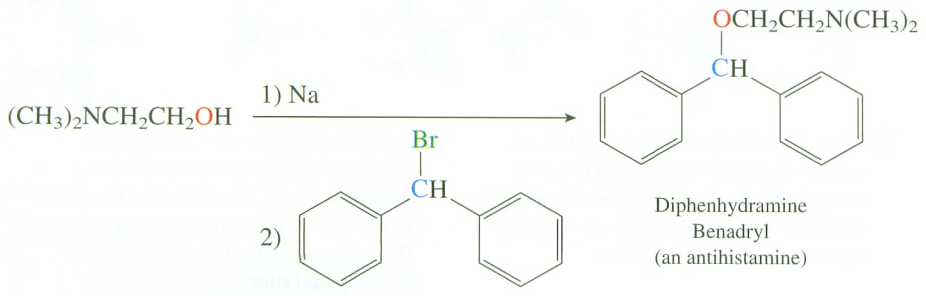
In equations like this, the reagents over the arrow are added in a sequence of separate steps, not all at once. Thus, in step 1, sodium metal is added to excess hexanol, which is both a reactant and the solvent for the reaction. Only after the reaction of the sodium and the alcohol is complete and the conjugate base of the alcohol has formed is the reagent shown in step 2 added. In the second step, the alkoxide ion acts as a nucleophile, replacing the leaving group of iodoethane to form the ether.







2,4-Dichlorophenoxyacetic acid
(2,4-D, an important herbicide)

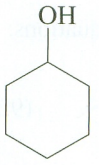


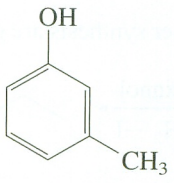
Diphenhydramine
Benadryl
(an antihistamine)

PROBLEM 10.5

Show the products of these reactions:

a) $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}H_2 + CH_3CH_2O^- \xrightarrow{EtOH}$

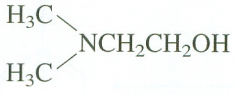
b)  $\xrightarrow[2)\ CH_3I]{1)\ Na}$

c)  $\xrightarrow[EtOH]{NaOH}$ $CH_3CH_2CH_2\underset{\displaystyle Cl}{\underset{|}{C}}H_2 \longrightarrow$

BioLink

PROBLEM 10.6

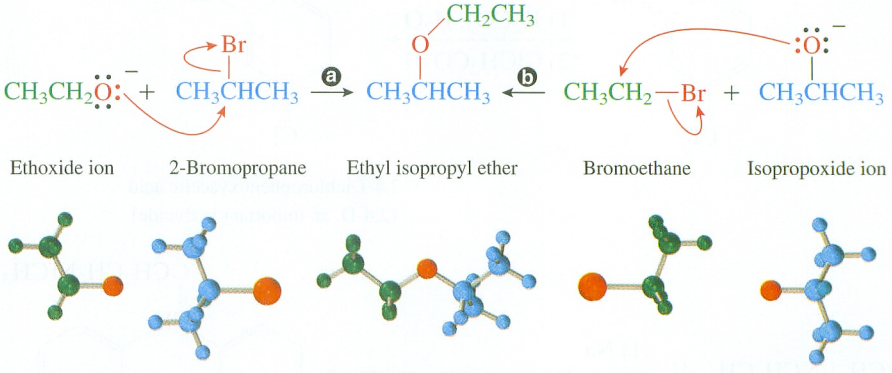
Diphenhydramine can also be synthesized by heating bromodiphenylmethane with the amino alcohol shown here. Offer a reason why the oxygen, rather than the nitrogen, of this compound acts as the nucleophile. What factor favors the N? What factor favors the O? Which factor is winning in this case?



An unsymmetrical ether can usually be prepared by two different Williamson ether syntheses. For example, the preparation of ethyl isopropyl ether could be accomplished by the reaction of ethoxide ion (nucleophile) with isopropyl bromide (electrophile) or by the reaction of isopropoxide ion (nucleophile) with ethyl bromide (electrophile), as shown in Figure 10.2. Which of these routes is better? Because alkoxide ions are strong

Figure 10.2

TWO POSSIBLE SYNTHESES OF ETHYL ISOPROPYL ETHER.



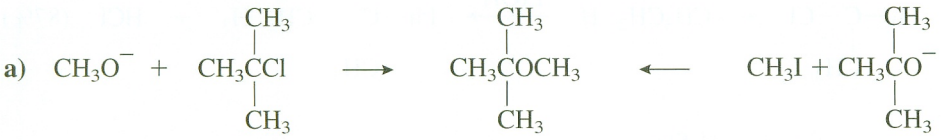
ⓐ This reaction has the bromine attached to a secondary carbon. With a strong base like ethoxide ion, the major reaction is elimination (E2) rather than substitution (S_N2), resulting in a poor yield of the desired ether.

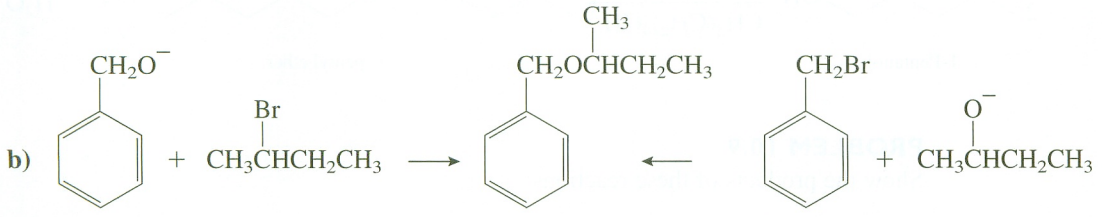
ⓑ In contrast, the bromine is attached to a primary carbon in this reaction. Much less elimination occurs, and the yield of the desired ether is higher here than in the other reaction. This is a better method for the synthesis of ethyl isopropyl ether.

bases, an unacceptable amount of elimination occurs if the leaving group is attached to a secondary carbon. Therefore, the route using the primary halide (ethyl bromide) will give a higher yield of the substitution product.

PROBLEM 10.7

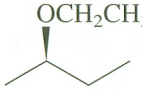
Explain which route would provide a better synthesis of these ethers:





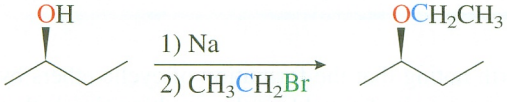
PRACTICE PROBLEM 10.1

Show a method for synthesizing this ether from an alcohol and an alkyl halide:



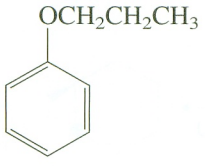
Solution

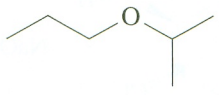
To minimize competing elimination by the E2 mechanism, treat the conjugate base of the secondary alcohol with the primary alkyl halide:



PROBLEM 10.8

Suggest a synthesis of these ethers starting with an alcohol and an alkyl halide:

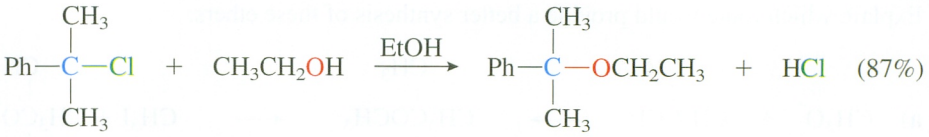
a) $CH_3OCH_2CH_2CH_2CH_3$ b) 

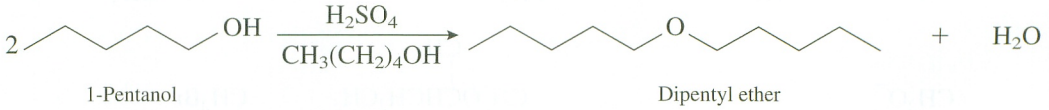
c) 

Ethers can also be prepared by using alcohols as the nucleophiles:

If the leaving group is bonded to a secondary or tertiary carbon, the reaction usually follows the S_N1 mechanism and is the preferred method in order to avoid problems with

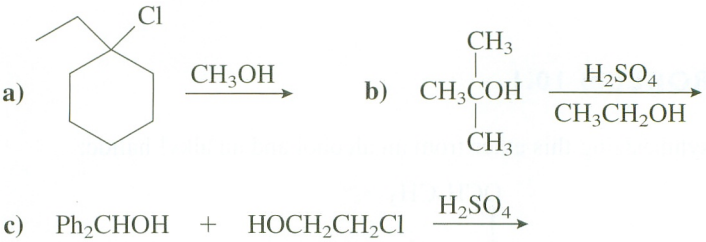
elimination. An alcohol must also be used as the nucleophile when the reaction is run under acidic conditions because alkoxide ions cannot exist in acid. Examples are provided by the following equations. In the first example, in which ethanol is the solvent, the reaction is an **ethanolysis.**





PROBLEM 10.9

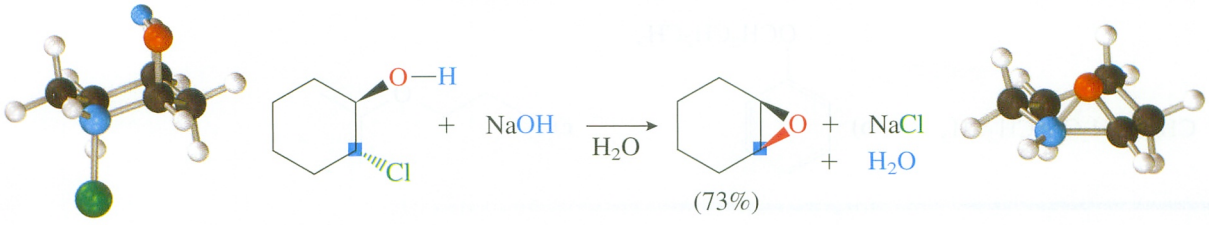
Show the products of these reactions:

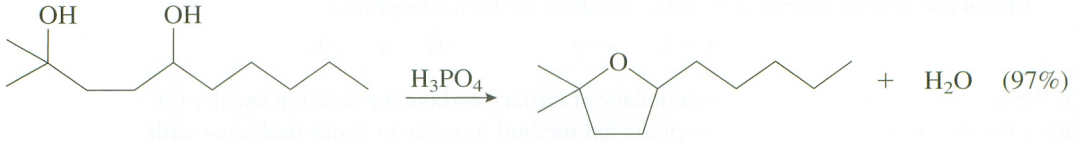


PROBLEM 10.10

Show all the steps in the mechanism for the reaction of 1-pentanol with sulfuric acid to form dipentyl ether.

Finally, it is worth noting that the formation of cyclic ethers by intramolecular nucleophilic substitutions is quite favorable if the resulting ring is three, five, or six membered, as shown in the following reactions:



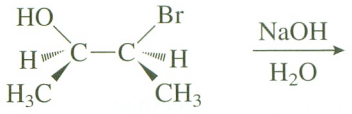


PROBLEM 10.11

Show the steps in the mechanism for the reaction of *trans*-2-chlorocyclohexanol with sodium hydroxide shown in the previous equation. Explain why *cis*-2-chlorocyclohexanol does not give a similar reaction.

PROBLEM 10.12

Show the product, including stereochemistry, for this reaction:

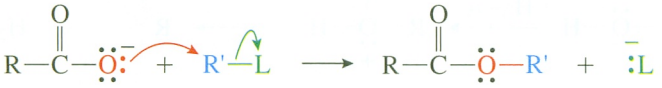


PROBLEM 10.13

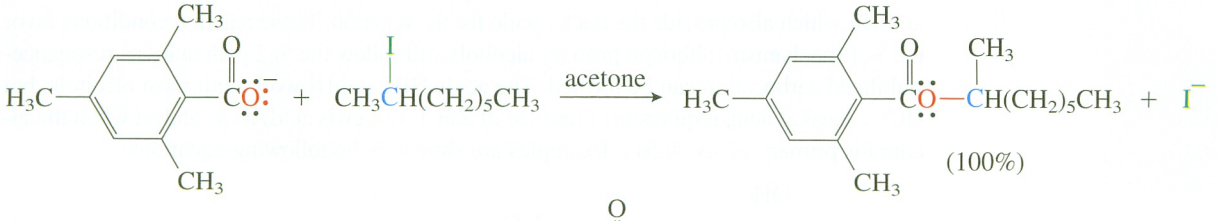
Because of the acidic conditions, this reaction proceeds by an S_N1 mechanism. Which hydroxy group acts as the leaving group in the reaction? Show all the steps in the mechanism for this reaction:

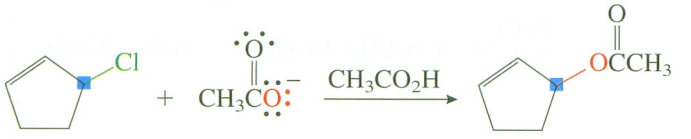
10.4 PREPARATION OF ESTERS

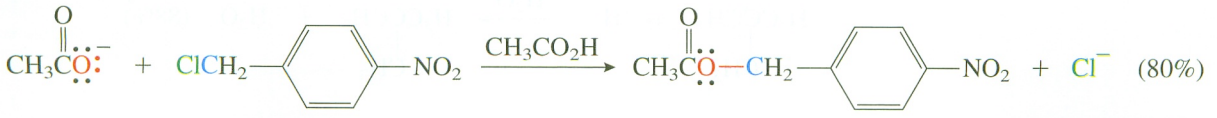
Esters can be prepared by employing carboxylate salts as nucleophiles, as shown in the following equation:



Because carboxylate salts are only weakly basic, elimination is not a problem when the leaving group is attached to a primary or secondary carbon. Several examples are provided in the following equations:

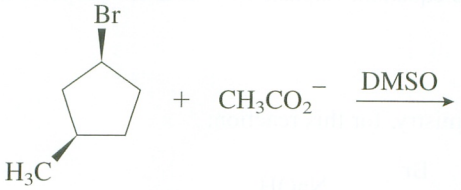


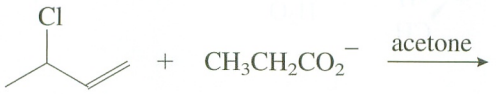


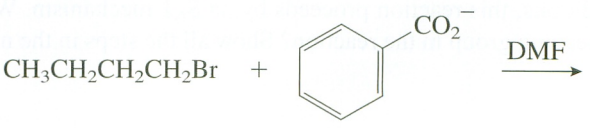


PROBLEM 10.14

Show the products of these reactions:

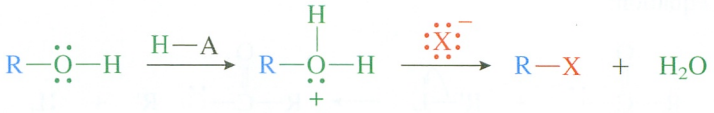
a) 

b) 

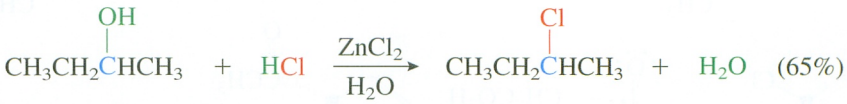
c) 

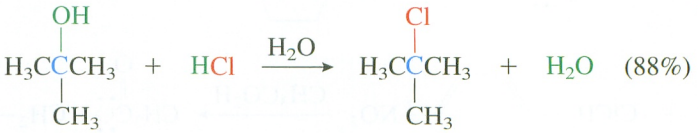
10.5 PREPARATION OF ALKYL HALIDES

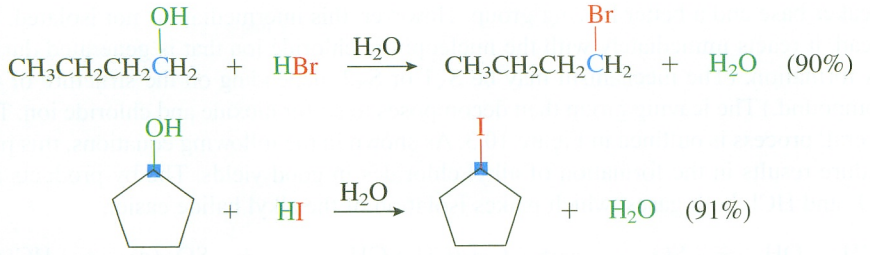
The preparation of alkyl halides by substitution reactions usually starts from alcohols because alcohols are widely available. Hydroxide ion is a poor leaving group, so the OH must first be converted into a better leaving group, either by protonation in acid or by conversion to a sulfonate or similar ester (see Section 8.9), as illustrated in the following equations:



Protonation of the alcohol can be accomplished by using the halogen acids, HCl, HBr, and HI, which also provide the nucleophile for the reaction. These reaction conditions favor the S_N1 mechanism, although primary alcohols still follow the S_N2 path unless a resonance-stabilized carbocation can be formed. The acids HBr and HI work with most alcohols, but HCl, a weaker acid, requires the presence of $ZnCl_2$ (a Lewis acid) as a catalyst when the alcohol is primary or secondary. Examples are shown in the following equations:





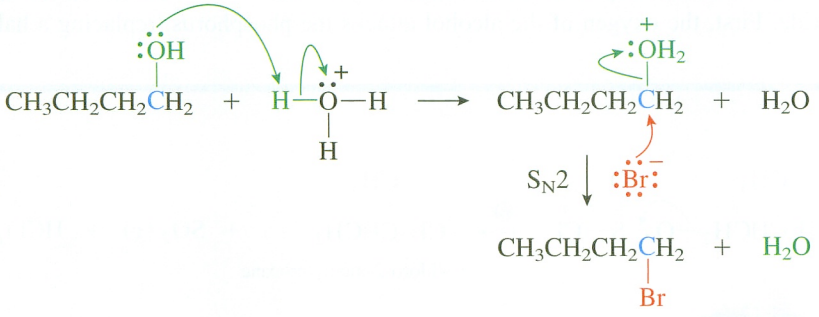


PRACTICE PROBLEM 10.2

Show all the steps in the mechanism for the reaction of 1-butanol with HBr in water.

Solution

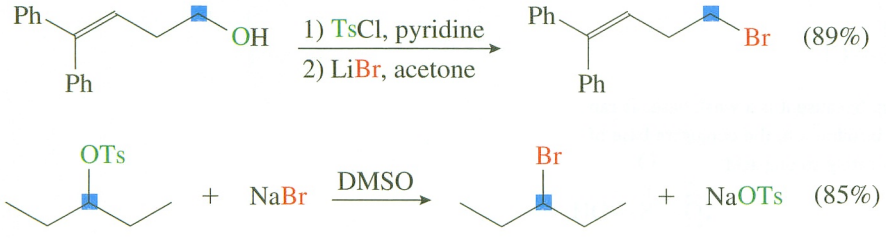
The reactant is a primary alcohol, so the mechanism must be S_N2. First the hydroxy group is protonated. Then bromide ion acts as a nucleophile.



PROBLEM 10.15

Show all the steps in the mechanism for the reaction of 2-methyl-2-butanol with HCl in water.

Conversion of the alcohol into a sulfonate ester followed by an S_N2 substitution using a halide nucleophile is another method that is commonly employed. Examples are provided in the following equations:

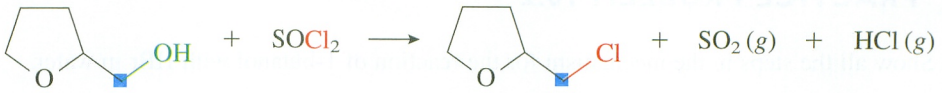


The sulfonate ester method requires two steps for the conversion of an alcohol into an alkyl chloride. A reagent that can accomplish this transformation in one step is thionyl chloride, $SOCl_2$. In a reaction very similar to the formation of sulfonate esters, this reagent replaces the hydrogen of the alcohol with a group that makes the oxygen a

weaker base and a better leaving group. However, this intermediate is not isolated. Instead, it reacts immediately with the nucleophilic chloride ion that is generated during its formation. (The mechanism may be S_N1 or S_N2, depending on the structure of the compound.) The leaving group then decomposes to sulfur dioxide and chloride ion. The overall process is outlined in Figure 10.3. As shown in the following equations, this procedure results in the formation of alkyl chlorides in good yields. The by-products are SO_2 and HCl, both gases, which makes isolation of the alkyl halide easier.

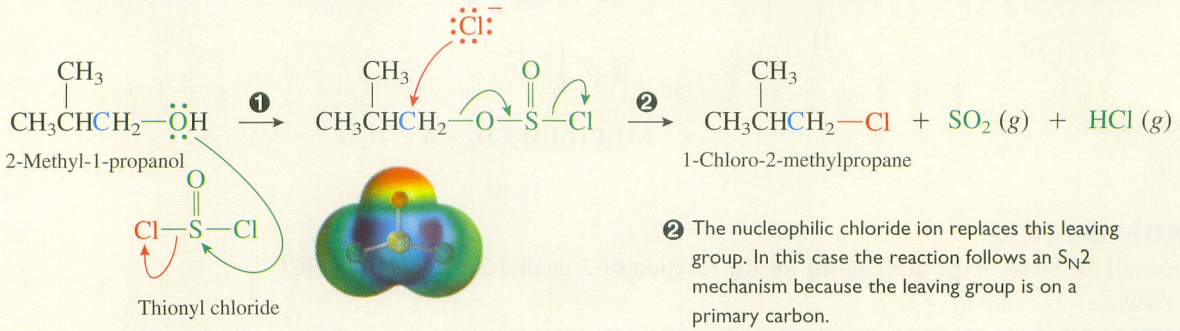
$$CH_3(CH_2)_4CH_2{-}OH + SOCl_2 \longrightarrow CH_3(CH_2)_4CH_2{-}Cl + SO_2\,(g) + HCl\,(g)$$

(61%)

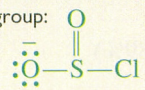


(75%)

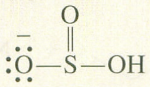
The reagents PBr_3 and PI_3 can be used to convert alcohols to alkyl bromides and alkyl iodides in one step. The reactions are very similar to those described for thionyl chloride. First, the oxygen of the alcohol attacks the phosphorus, replacing a halogen



❶ In a reaction very similar to the formation of a sulfonate ester (see Section 8.9), the oxygen of the alcohol displaces the chlorine. (The mechanism for this part of the reaction may involve more than one step, but the details are not important at this point.) The by-product is hydrogen chloride. This converts the oxygen to the chlorofulfite leaving group:



This ion is a good leaving group because it is a weak base, as can be seen by its resemblance to bisulfite ion, the conjugate base of sulfurous acid, which is a moderately strong acid with a pK_a of 1.9:



Bisulfite ion

❷ The nucleophilic chloride ion replaces this leaving group. In this case the reaction follows an S_N2 mechanism because the leaving group is on a primary carbon.

Figure 10.3

MECHANISM OF THE REACTION OF AN ALCOHOL WITH THIONYL CHLORIDE TO PRODUCE AN ALKYL CHLORIDE.

and making the oxygen a better leaving group. Then the halide ion replaces this leaving group to produce the alkyl halide product. Several examples are provided in the following equations:

$$CH_3CH_2CH_2CH_2{-}OH \xrightarrow{PBr_3} CH_3CH_2CH_2CH_2{-}Br \quad (93\%)$$

$$CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3 \xrightarrow{PBr_3} CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 \quad (90\%)$$

$$CH_3CH_2CH_2{-}OH \xrightarrow{PI_3} CH_3CH_2CH_2{-}I \quad (90\%)$$

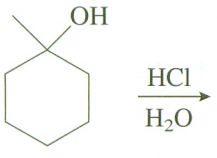
A final method sometimes employed to prepare alkyl halides uses an S_N2 reaction with one halogen as the leaving group and a different halide ion as the nucleophile, as shown in the following general equation:

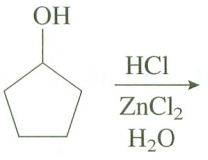
However, this is an equilibrium reaction; the product can react with the displaced halide ion and reform the starting material. If the reaction is to be useful in synthesis, some method must be found to favor the product at equilibrium. If acetone is used as the solvent, the reaction of sodium iodide with alkyl chlorides or bromides can be used to prepare alkyl iodides. In this case the equilibrium favors the alkyl iodide because sodium chloride and sodium bromide (but not sodium iodide) are insoluble in acetone and precipitate, thus driving the equilibrium to the right according to Le Chatelier's principle.

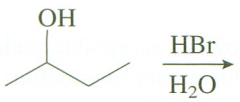
$$CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2C{\equiv}N + NaI \xrightarrow{\text{acetone}} CH_3\underset{\displaystyle I}{\underset{|}{C}}HCH_2C{\equiv}N + NaBr\,(s) \quad (96\%)$$

PROBLEM 10.16

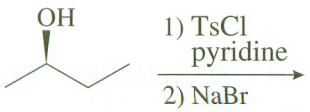
Show the products of these reactions:

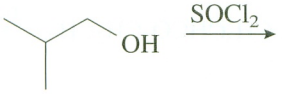
a) 

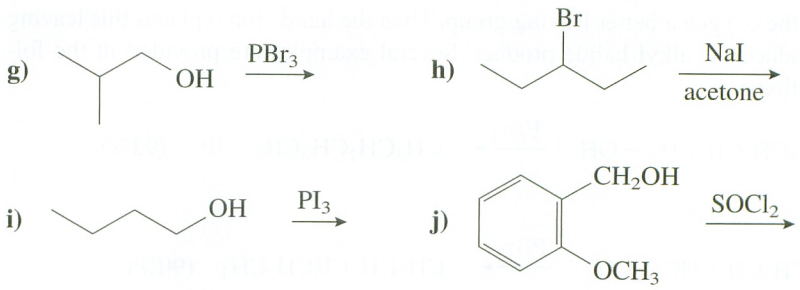
b) 

c) 

d) $CH_3CH_2CH_2OH \xrightarrow[H_2O]{HI}$

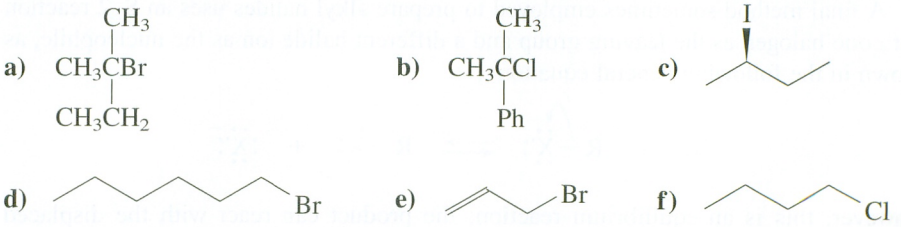
e) 

f) 



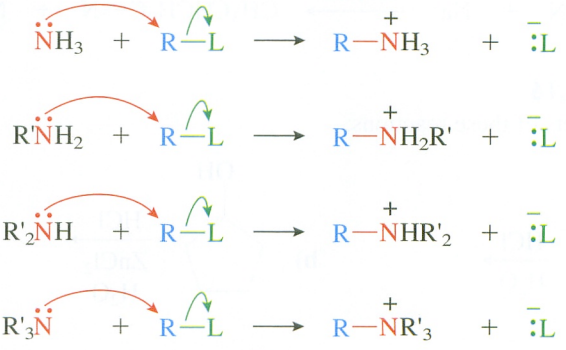
PROBLEM 10.17

Suggest reagents that could be used to prepare these alkyl halides from alcohols:

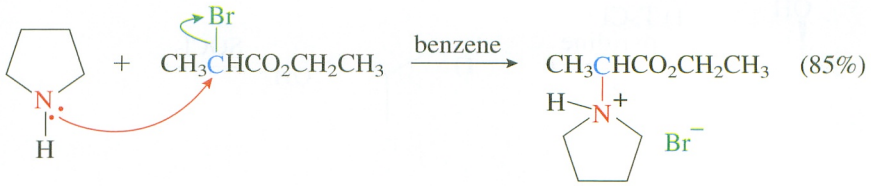


10.6 PREPARATION OF AMINES

Ammonia and unhindered amines are good nucleophiles. Therefore, it would appear that amines should be readily prepared by reacting these nucleophiles with the appropriate alkyl halide or sulfonate ester in an S_N2 reaction, according to the following general equations:



As illustrated in the following reaction, this method provides acceptable yields of tertiary amines, using secondary amines as nucleophiles. Quaternary ammonium salts can also be prepared from tertiary amines as nucleophiles.



However, this reaction is much less useful when ammonia is the nucleophile because the initial product, a primary amine, is a stronger base and a stronger nucleophile than is ammonia. Therefore, the primary amine preferentially reacts as the nucleophile, producing a secondary amine as a by-product (see Figure 10.4). This problem is termed **multiple alkylation** because more than one alkyl group becomes attached to the nucleophile. Even when a large excess of ammonia is used to favor its reaction as the nucleophile, a significant amount of secondary amine is often formed. For similar reasons the use of a primary amine as the nucleophile results in the formation of a tertiary amine in addition to the desired secondary amine. (However, because of steric effects, a tertiary amine is not a stronger nucleophile than a secondary amine, so multiple alkylation is not a problem when a secondary amine is used as the nucleophile.)

PROBLEM 10.18

Show the products of these reactions:

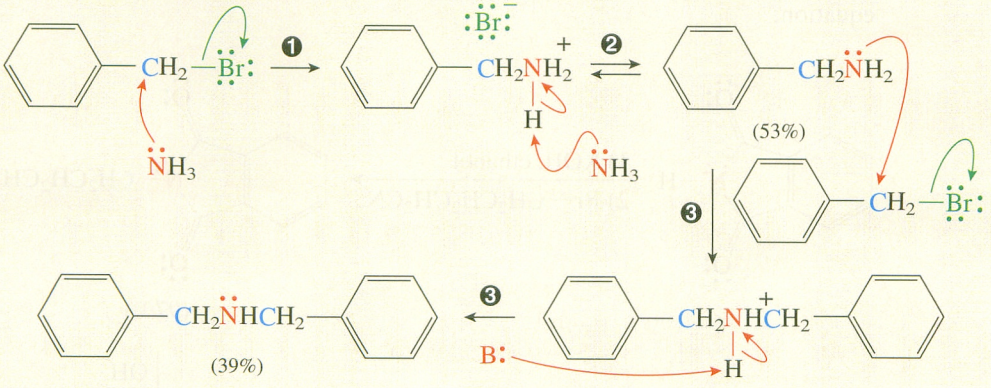
a) $(CH_3CH_2)_2NH + CH_3CH_2Br \xrightarrow{CH_3OH}$

b) $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{N}}CH_3 + CH_3I \xrightarrow{\text{ether}}$

❶ Ammonia acts as the nucleophile in an S_N2 reaction, replacing the bromine.

❷ In an equilibrium process, the resulting ammonium salt can lose a proton to a base such as ammonia to produce a primary amine. The primary amine is a stronger base and, therefore, a better nucleophile than ammonia.

❸ Even when a large excess of ammonia is present, some of the primary amine reacts to produce a secondary amine.

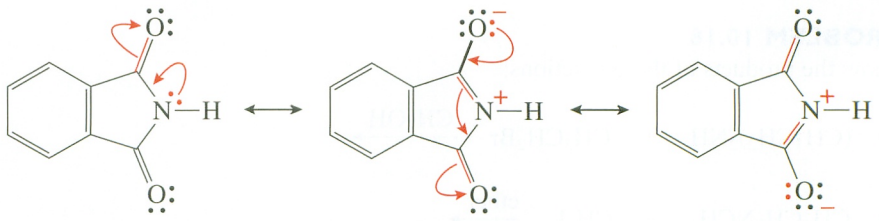


In this particular case, in which an eightfold excess of ammonia is used, the product mixture consists of 53% of the primary amine and 39% of the secondary amine.

Figure 10.4

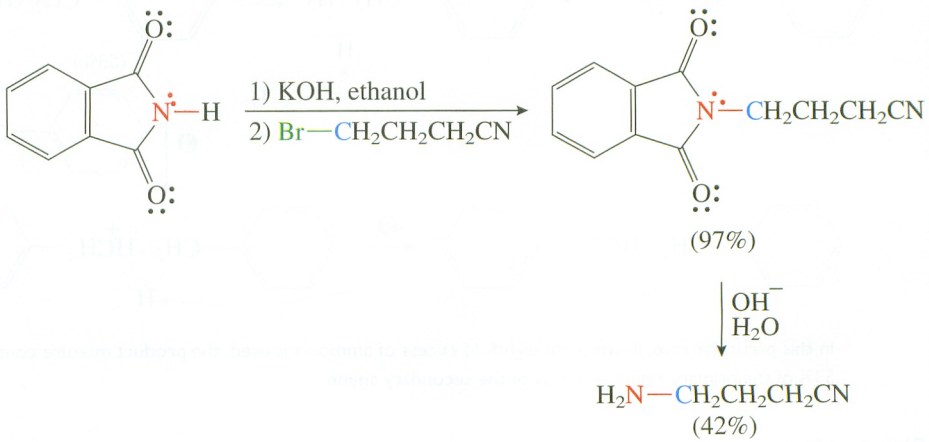
MECHANISM OF MULTIPLE ALKYLATION USING AMMONIA AS A NUCLEOPHILE.

Because of the problem of multiple alkylation when ammonia reacts with alkyl halides, a multistep method, called the Gabriel synthesis, has been developed to prepare primary amines. This procedure resembles the acetate method for preparing alcohols (Section 10.2) in that carbonyl groups are attached to the nitrogen to decrease its reactivity. After the substitution has been accomplished, the carbonyl groups are removed to provide the desired primary amine. In the Gabriel synthesis the synthetic equivalent for ammonia is phthalimide. (An imide has two carbonyl groups bonded to the nitrogen.) The electrons on the nitrogen of phthalimide are not very basic or nucleophilic because of resonance involving both carbonyl groups:



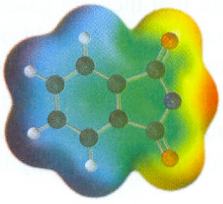
Phthalimide

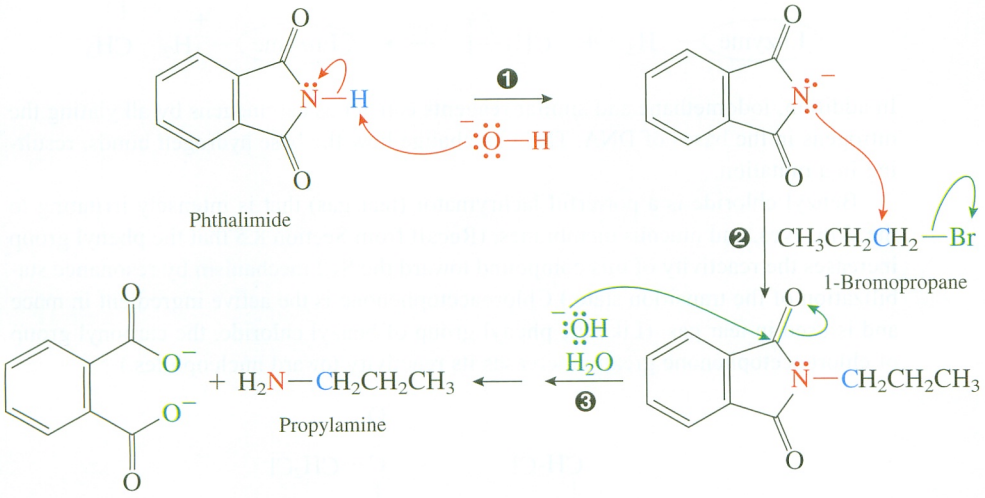
Therefore, the proton on the nitrogen must be removed to use this nitrogen as a nucleophile. This hydrogen is relatively acidic (pK_a = 9.9) because of resonance stabilization of the conjugate base, similar to that shown for phthalimide. Hydroxide ion is a strong enough base to remove this proton and generate the conjugate base of phthalimide. The reaction of this nucleophile with an alkyl halide or an alkyl sulfonate ester, by an S_N2 mechanism, produces a substituted phthalimide with an alkyl group bonded to the nitrogen. The electrons on the nitrogen of this alkylated phthalimide are not nucleophilic, so there is no danger of multiple alkylation. The carbonyl groups are then removed to give the desired primary amine in a reaction that is very similar to the ester hydrolysis described in Figure 10.1. The process is outlined in Figure 10.5 and an additional example is provided by the following equation:



❶ Because of resonance, the electron pair on the nitrogen of phthalimide is not very basic or nucleophilic. The hydrogen on the nitrogen is much more acidic than a hydrogen of a normal amine because the conjugate base is stabilized by resonance. It is acidic enough to be removed completely by a base such as hydroxide ion.

❷ The resulting phthalimide anion is a good nucleophile in the S_N2 reaction.





❸ The desired amine is generated by reaction of the phthalimide with an aqueous base. The conditions are very similar to those of the ester cleavage shown in Figure 10.1. Again, the mechanism begins by attack of a hydroxide ion nucleophile at the electrophilic carbonyl carbon, ultimately breaking the bond between the carbonyl carbon and the nitrogen. (The mechanism for this reaction is covered in detail in Chapter 19.) A similar reaction occurs at the other carbonyl carbon. Overall, phthalimide is a synthetic equivalent for ammonia.

Like phthalimide itself, the alkylated phthalimide is not nucleophilic, so there is no problem with multiple alkylation occurring. The next step of the process is to replace the carbonyl groups on the nitrogen with hydrogens.

Figure 10.5

THE GABRIEL SYNTHESIS OF A PRIMARY AMINE.

Focus On Biological Chemistry

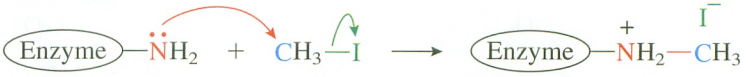
Biological Alkylations and Poisons

Many of the reagents that are routinely used as substrates for S_N2 reactions in the laboratory are poisonous and must be used with caution. These compounds have a leaving group bonded to an unhindered carbon, so they are very reactive toward nucleophiles. They are called *alkylating agents* because they attach an alkyl group to the nucleophile.

Iodomethane is a prime example of a reactive alkylating agent. Because of its lack of steric hindrance and excellent leaving group, it is very reactive toward nucleophiles.

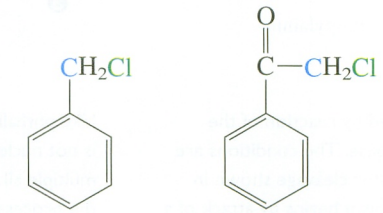
Continued

It is a common reagent and often is the first choice when a chemist desires to attach a methyl group to a nucleophile. (Bromomethane and chloromethane might serve as well except that they are gases at room temperature and are therefore much more difficult to handle than liquid iodomethane.) Like the other reactive alkylating agents, iodomethane is poisonous because it reacts with nucleophiles, such as NH_2 and SH groups, in the organism, attaching a methyl group to them. Iodomethane can deactivate an enzyme and interfere with its biological function by alkylating a nucleophile at the active site and changing its nucleophilicity:



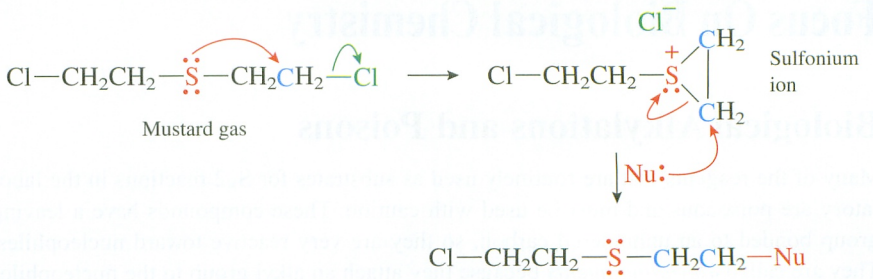
In addition, iodomethane and similar reagents can act as carcinogens by alkylating the nitrogens in the bases of DNA. This can change how the base hydrogen bonds, resulting in a mutation.

Benzyl chloride is a powerful lachrymator (tear gas) that is intensely irritating to the skin, eyes, and mucous membranes. (Recall from Section 8.5 that the phenyl group increases the reactivity of this compound toward the S_N2 mechanism by resonance stabilization of the transition state.) Chloroacetophenone is the active ingredient in mace and is used in tear gas. (Like the phenyl group of benzyl chloride, the carbonyl group of chloroacetophenone greatly increases its reactivity toward nucleophiles.)



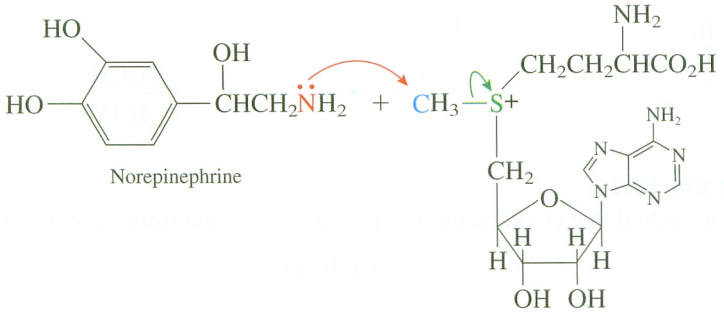
Benzyl chloride Chloroacetophenone

One of the most infamous reactive alkylating agents is mustard gas, which was used as a chemical warfare agent during World War I. The sulfur of mustard gas acts as an intramolecular nucleophile to generate a cyclic sulfonium ion that is even more reactive as an alkylating agent. Note that it has two reactive electrophilic sites in each molecule. In heavy doses it can cause blindness and death, but its delayed effects, including cough; respiratory damage; and reddening, itching, and blistering of the skin, are more insidious.



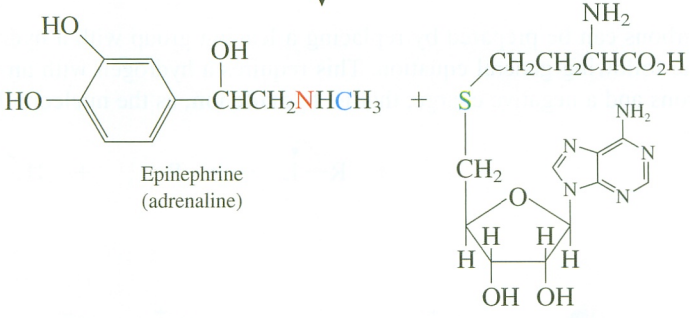
Mustard gas

When we desire to attach a methyl group to a nucleophile in the laboratory, we often choose a simple reagent such as iodomethane. Living organisms cannot use this reagent because it is too reactive and too indiscriminate. Iodomethane will react with almost any nucleophile. Nature's iodomethane is a much more complex molecule called *S*-adenosylmethionine, or SAM. The leaving group in SAM is a disubstituted sulfur atom and confers just the right reactivity on the compound. SAM is used to methylate the nitrogen of norepinephrine in the biosynthesis of epinephrine (adrenaline) and also serves as the methylating agent in the biosynthesis of the important lipid phosphatidylcholine (lecithin) from phosphatidylethanolamine.

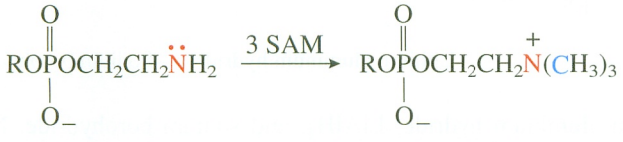


Norepinephrine

S-Adenosylmethionine (SAM)



Epinephrine (adrenaline)

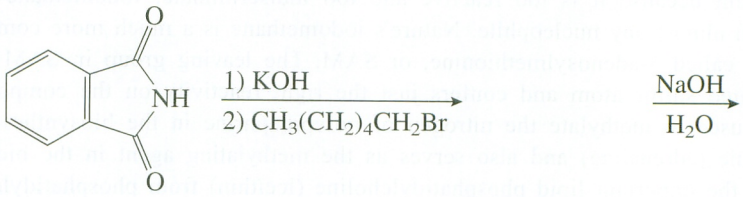


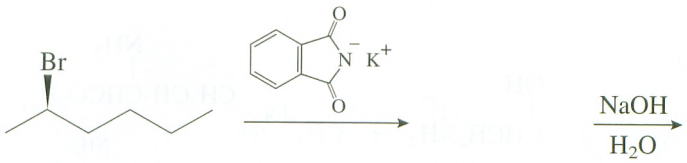
Phosphatidylethanolamine

Phosphatidylcholine

PROBLEM 10.19

Show the products of these reactions:

a) 

b) 

PROBLEM 10.20

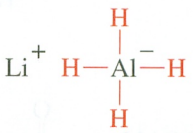
Suggest a method that could be used to prepare this amine from an alkyl halide:

$$PhCH_2CH_2NH_2$$

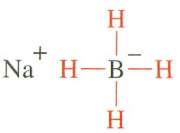
10.7 PREPARATION OF HYDROCARBONS

Hydrocarbons can be prepared by replacing a leaving group with a hydrogen, according to the following general equation. This requires a hydrogen with an unshared pair of electrons and a negative charge, that is, **hydride ion,** as the nucleophile.

Hydride ion



Lithium aluminum hydride



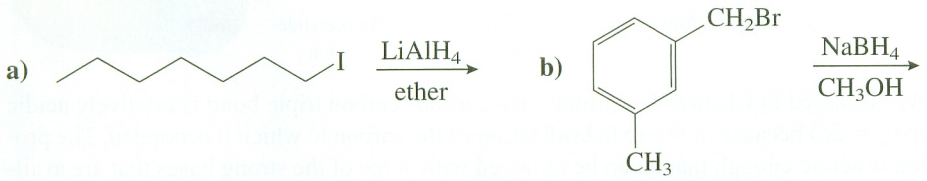
Sodium borohydride

Both lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, react as though they contain a nucleophilic hydride ion, although the hydrogens are covalently bonded to the metal atoms, either aluminum or boron. However, hydrogen is more electronegative than either of these metals, resulting in each hydrogen having a partial negative charge. Because of this polarization, the compounds react as sources of hydride ion. Lithium aluminum hydride is a very reactive compound and reacts vigorously (often explosively) with even weakly acidic compounds such as water and alcohols. It must be used in inert solvents such as ethers. Sodium borohydride is much less reactive and is often used in alcohols or alkaline water as solvent. With either reagent the reactions have the usual S_N2 limitations; that is, they work well only when the leaving group is

bonded to a primary or secondary carbon. The following equations provide examples of the use of these reagents to replace a leaving group with hydrogen:

PROBLEM 10.21

Show the products of these reactions:

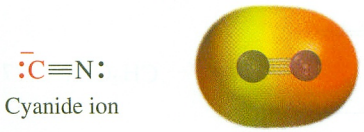


10.8 Formation of Carbon–Carbon Bonds

Reactions that form carbon–carbon bonds are of great importance in organic synthesis because they enable smaller compounds to be converted to larger compounds. Forming these bonds by nucleophilic substitution reactions requires a carbon nucleophile—a **carbanion** (carbon anion), as shown in the following general equation:

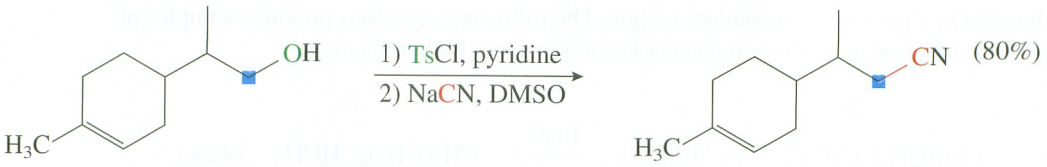
Two useful carbon nucleophiles are introduced in this section. Other important carbon nucleophiles are discussed in later chapters, especially Chapter 20.

The first of these carbon nucleophiles, **cyanide ion,** is a moderate base and a good nucleophile:

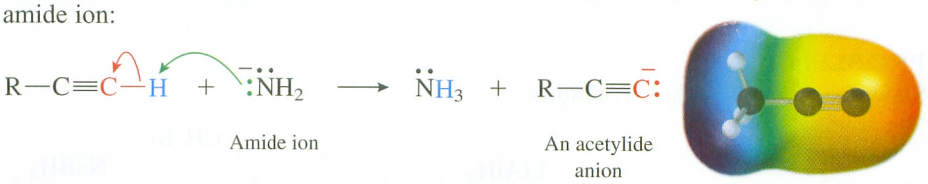


Cyanide ion

Cyanide ion reacts by the S_N2 mechanism and aprotic solvents are often employed to increase its reactivity. Yields of substitution products are excellent when the leaving group is attached to a primary carbon. Because of competing elimination reactions, yields are lower, but still acceptable, for secondary substrates. As expected for an S_N2 process, the reaction does not work with tertiary substrates. Substitution with cyanide ion adds one carbon to the compound while also providing a new functional group for additional synthetic manipulation. Some examples are given in the following equations:

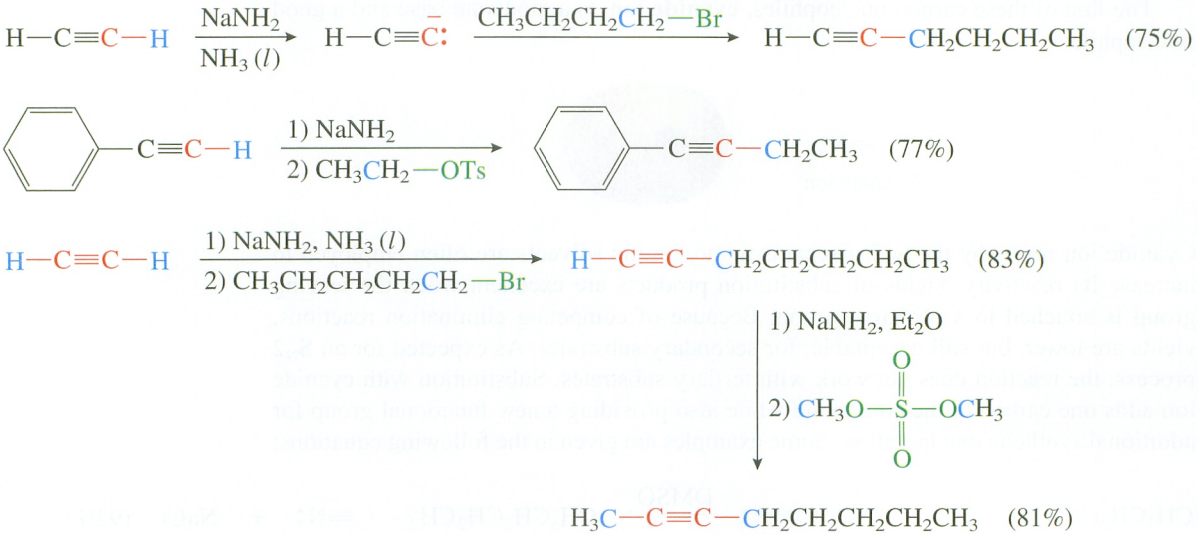


A second group of important carbon nucleophiles are the **acetylide anions**. These nucleophiles are generated by treating 1-alkynes with a very strong base, such as amide ion:



As discussed in Chapter 4, a proton on a carbon–carbon triple bond is relatively acidic ($pK_a = 25$) because of the *sp* hybridization of the carbon to which it is bonded. The proton is acidic enough that it can be removed with some of the strong bases that are available to the organic chemist. Usually, sodium amide ($NaNH_2$), the conjugate base of ammonia ($pK_a = 38$), often in liquid ammonia as the solvent, is used to remove the proton. Amide ion is a strong enough base so that the equilibrium in the above equation lies entirely to the right. (Note that carbanions generated by removing protons from sp^3- and sp^2-hybridized carbons are not generally available for use as nucleophiles in S_N2 reactions because the protons attached to them are not acidic enough to be removed in this manner.)

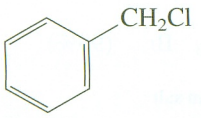
Because acetylide anions are strong nucleophiles, they react by the S_N2 mechanism. Good yields of substitution products are obtained only when the leaving group is attached to a primary carbon; secondary substrates give mainly elimination because the anion is also a strong base. Several examples are provided in the following equations. The last example shows how ethyne can be alkylated twice—both hydrogens can be replaced with alkyl groups in sequential steps!



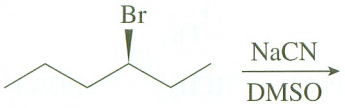
PROBLEM 10.22

Show the products of these reactions:

ORGANIC Chemistry Now™
Click *Coached Tutorial Problems* for more practice in drawing the products of the **Alkylation of Actetylide Anions.**

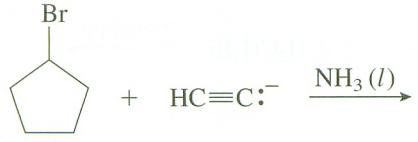
a) 

b) $CH_3C{\equiv}C{-}H \xrightarrow[2)\ CH_3CH_2CH_2Br]{1)\ NaNH_2,\ NH_3\ (l)}$

c) 

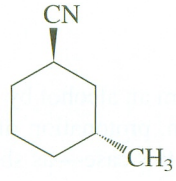
d) $HC{\equiv}CH \xrightarrow[2)\ CH_3CH_2Br]{1)\ NaNH_2,\ NH_3\ (l)} \xrightarrow[2)\ CH_3I]{1)\ NaNH_2}$

e)

f) 

PROBLEM 10.23

Suggest methods for preparing these compounds from alkyl halides:

a) 

b) $HC{\equiv}CCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

c) $CH_3C{\equiv}CCH_2Ph$

10.9 Phosphorus and Sulfur Nucleophiles

Sulfur occurs directly beneath oxygen in the periodic table. Therefore, sulfur compounds are weaker bases but better nucleophiles than the corresponding oxygen compounds. Sulfur compounds are excellent nucleophiles in S_N2 reactions, and because they are relatively weak bases, elimination reactions are not usually a problem. Yields are good with primary and secondary substrates. For similar reasons, phosphorus compounds also give good yields when treated with primary and secondary substrates in S_N2 reactions. The following equations provide examples of the use of these nucleophiles:

$$CH_3{-}\ddot{S}:^- + Cl{-}CH_2CH_2OH \xrightarrow{\text{ethanol}} CH_3{-}\ddot{S}{-}CH_2CH_2OH + Cl^- \quad (80\%)$$

$$:\ddot{S}:^{2-} + 2\,CH_3CH_2CH_2{-}Br \xrightarrow{\text{ethanol}} CH_3CH_2CH_2{-}S{-}CH_2CH_2CH_3 + 2\,Br^- \quad (85\%)$$

$$Ph_3P: + CH_3{-}Br \xrightarrow{\text{benzene}} Ph_3\overset{+}{P}{-}CH_3\ Br^- \quad (99\%)$$

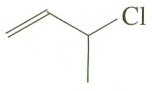
Triphenylphosphine — A phosphonium salt

$$Ph_3P: + PhCH{=}CHCH_2(Cl) \xrightarrow{\text{xylene}} PhCH{=}CH\underset{\displaystyle PPh_3^+}{CH_2}\ Cl^- \quad (92\%)$$

Triphenylphosphine is probably the most important phosphorus nucleophile for organic chemists because it produces phosphonium salts (see the preceding two equations). These phosphonium salts are starting materials for an important preparation of alkenes that will be discussed in Chapter 18.

PROBLEM 10.24

Show the products of these reactions:

a)  $+\ PhS^-Na^+ \xrightarrow{CH_3OH}$

b) $Ph_3P + CH_3CH_2CH_2Br \xrightarrow{\text{benzene}}$

c) $CH_3CH_2CH_2CH_2S^- + CH_3I \xrightarrow{EtOH}$

d) $NaSCH_2CH_2SNa + BrCH_2CH_2Br \xrightarrow{CH_3OH}$

10.10 Ring Opening of Epoxides

Section 8.9 discussed the generation of a leaving group, water, from an alcohol by protonation of the oxygen of the hydroxy group. In a similar fashion, protonation of the oxygen of an ether also generates a leaving group—an alcohol in this case—as shown in the following equation:

$$R{-}\ddot{O}{-}R' \xrightarrow{H{-}A} R{-}\overset{H}{\overset{|}{\overset{+}{O}}}{-}R' \xrightarrow{:\bar{N}u} R{-}\ddot{O}{-}H + R'{-}Nu$$

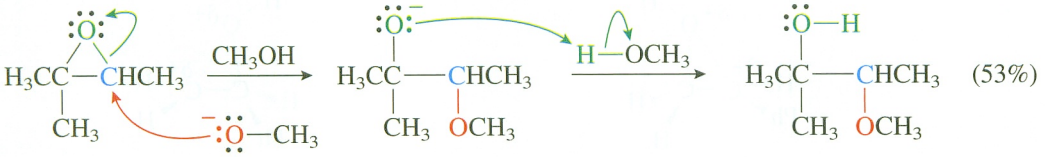
This reaction requires more vigorous conditions than the reaction of alcohols, resulting in low yields in many cases. For this reason the reaction is not commonly used in synthesis.

An **epoxide** (also known as an oxirane) is a three-membered cyclic ether:

An epoxide

Like cyclopropane, epoxides have a large amount of ring strain and are much more reactive than normal ethers. Because of this ring strain, one carbon–oxygen bond of an

epoxide can be broken in a nucleophilic substitution reaction. The following equation shows an example:

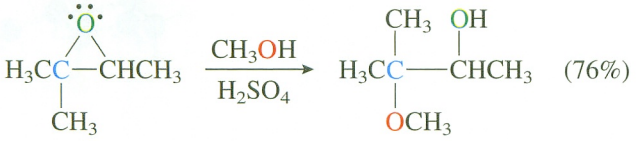


(53%)

Both of the carbons of the epoxide ring are electrophilic, so at first glance, either might be expected to react with the nucleophile, methoxide ion. However, reactions of epoxides under basic or neutral conditions, as in this case, usually follow an S_N2 mechanism. Therefore, the nucleophile reacts at the less hindered secondary carbon, with inversion of configuration.

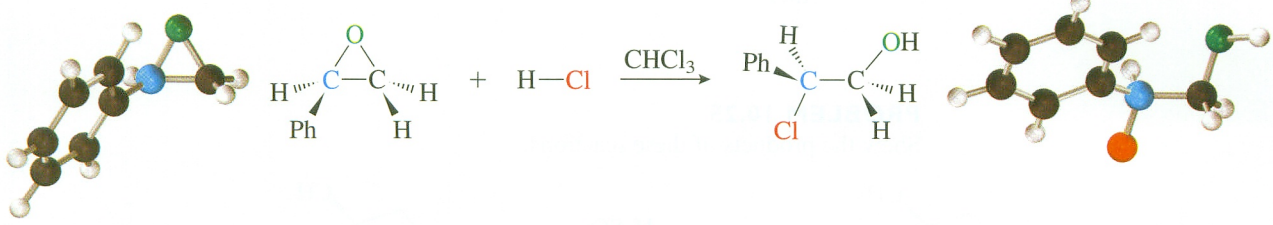
In the preceding reaction the leaving group (RO^-) is a very strong base. As discussed in Chapter 8, HO^- and RO^- are much too basic to act as leaving groups in normal nucleophilic substitution reactions. In the special case of epoxides, however, even RO^- can act as a leaving group because of the large amount of strain that is relieved when the carbon–oxygen bond is broken and the ring is opened.

Nucleophilic ring opening of epoxides can also be accomplished in acid solution. The oxygen is first protonated, making it a much better leaving group. Although these are typical S_N1 conditions, the actual mechanism is somewhere between S_N1 and S_N2—the reaction has characteristics of both mechanisms. The stereochemistry is that predicted for an S_N2 mechanism; the nucleophile approaches from the side opposite the leaving oxygen. The regiochemistry is that predicted for an S_N1 mechanism; the substitution occurs at the carbon that would be more stable as a carbocation. This often results in the carbon–oxygen bond that is broken under acidic conditions being different from the one that is broken under basic conditions, as can be seen by comparing the product in the following reaction with the one from the preceding reaction:



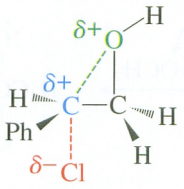
(76%)

Another example, in which it can be seen that the reaction proceeds with inversion of configuration, is provided in the following reaction:

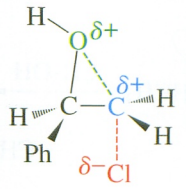


Because such reactions have features of both the S_N2 mechanism (stereochemistry) and the S_N1 mechanism (regiochemistry), they are said to follow a borderline S_N2 mechanism. The transition state geometry resembles that for an S_N2 reaction, but the bond to the leaving group is broken to a greater extent than the bond to the nucleophile is formed, resulting in considerable positive charge buildup on the carbon. Therefore, the transition state that has

this positive charge buildup on the carbon that would be the more stable carbocation is favored. The two possible transition states for the preceding reaction are as follows:

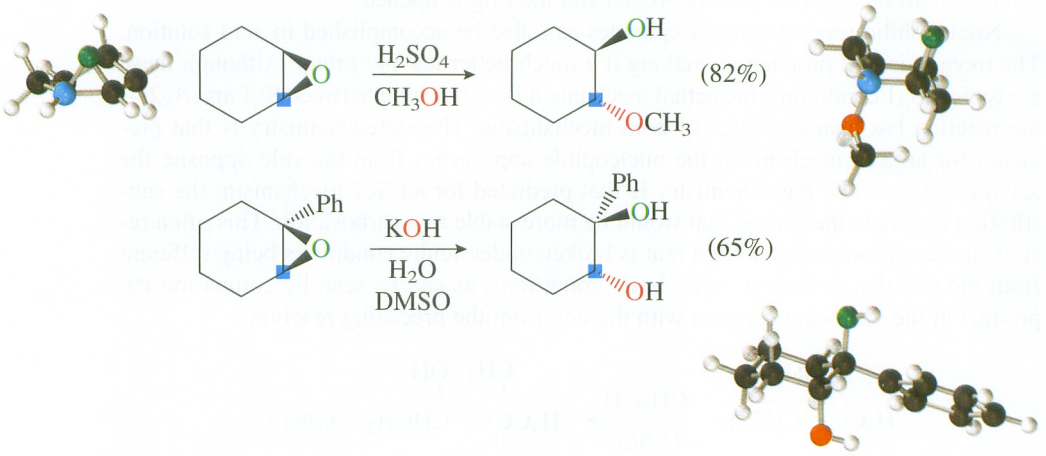


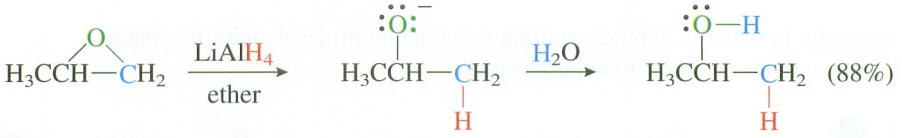
This transition state has a buildup of positive charge on the carbon attached to the phenyl group. The phenyl group helps stabilize the positive charge, making this transition state more stable. The reaction pathway resulting in the observed product proceeds through this transition state.



This transition state has a buildup of positive charge on the primary carbon, where it is less stable. As a result, no product is observed from this transition state.

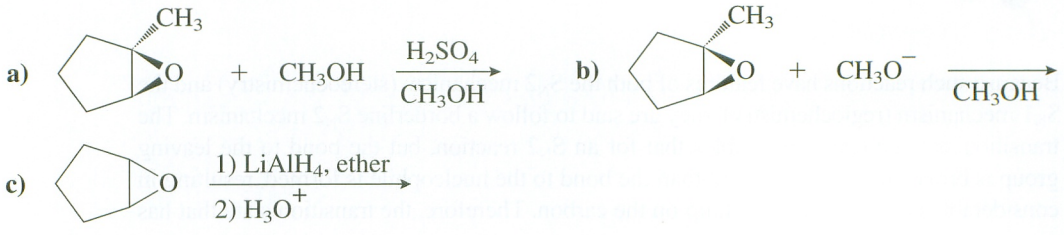
Other examples of nucleophilic substitutions on epoxides are given in the following equations:





PROBLEM 10.25

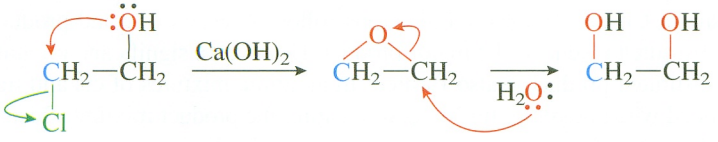
Show the products of these reactions:



Focus On

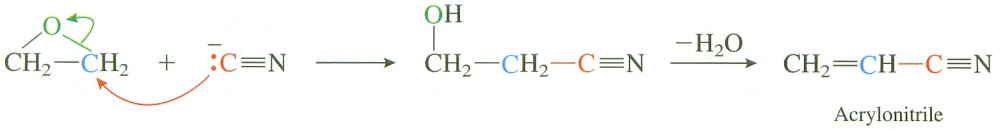
Uses of Epoxides in Industry

Epoxides are important intermediates in many industrial processes. For example, the reaction of the simplest epoxide, ethylene oxide, with water is employed to produce ethylene glycol, which is used in antifreeze and to prepare polymers such as Dacron. One method for the preparation of ethylene oxide employs an intramolecular nucleophilic substitution reaction of ethylene chlorohydrin:



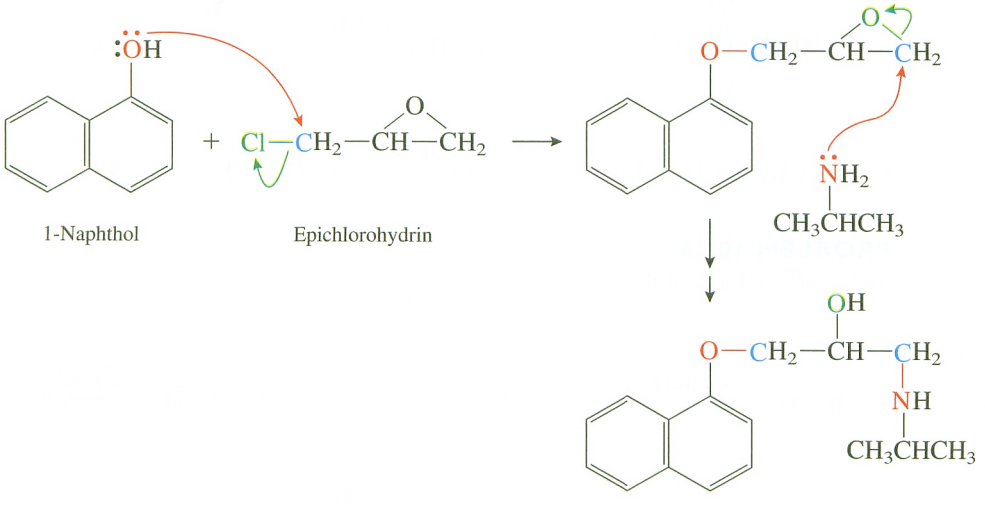
Ethylene chlorohydrin — Ethylene oxide — Ethylene glycol

Nucleophilic cyanide ion can also be used to open the epoxide ring. This reaction was employed in a now obsolete pathway for the preparation of acrylonitrile, which is used to make Orlon:



Acrylonitrile

Propranolol, a drug that is used to lower blood pressure, is prepared from the epoxide epichlorohydrin. First, the oxygen of 1-naphthol displaces the chlorine of epichlorohydrin in an S_N2 reaction. Then the epoxide ring is opened by the nucleophilic nitrogen of isopropylamine in another S_N2 reaction to form propranolol.



1-Naphthol — Epichlorohydrin

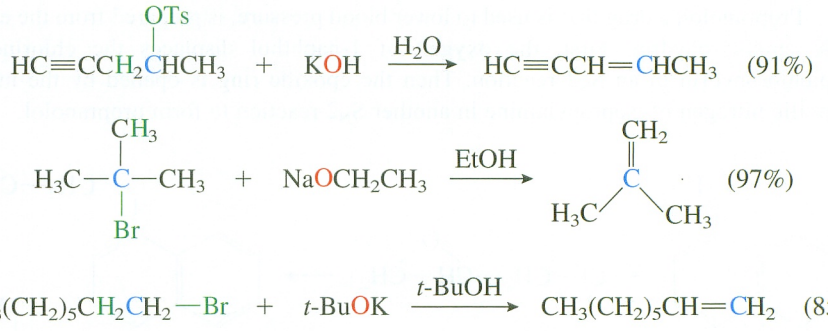
Propranolol

10.11 Elimination of Hydrogen Halide (Dehydrahalogenation)

Elimination reactions are a useful method for the preparation of alkenes, provided that certain limitations are recognized. One problem is the competition between substitution and elimination. The majority of eliminations are done under conditions that favor the E2 mechanism. In these cases, steric hindrance can be used to slow the competing S_N2 pathway. Tertiary substrates and most secondary substrates give good yields of the elimination product when treated with strong bases. Sterically hindered bases can be employed with primary substrates to minimize substitution.

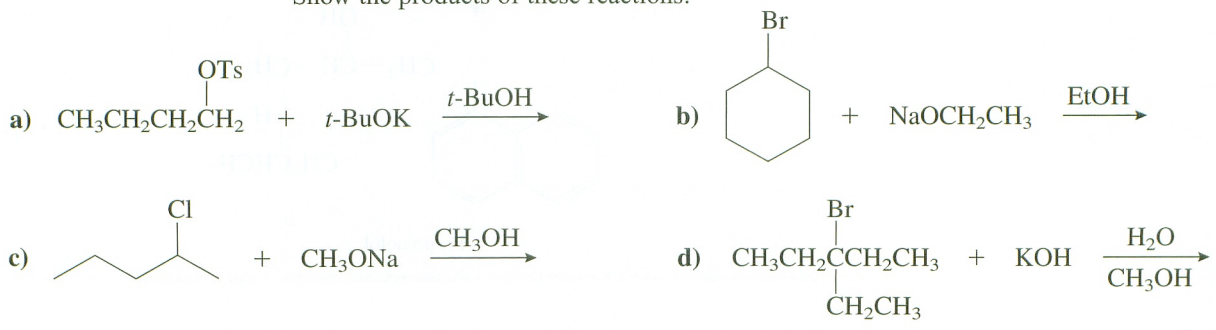
Another problem that occurs with eliminations is the regiochemistry of the reaction. As we saw in Chapter 9, most eliminations follow Zaitsev's rule and produce the more highly substituted alkene as the major product. However, a significant amount of the less highly substituted product is also formed. In addition, mixtures of cis and trans isomers are produced when possible, further complicating the product mixture. Because separating a mixture of such isomers is usually a difficult task, elimination reactions are often not the best way to prepare alkenes. (Other methods will be described in subsequent chapters.) However, if only one product can be formed, or if one is expected to greatly predominate in the reaction mixture, then these elimination reactions can be quite useful.

Thus, reaction of an alkyl halide with a strong base can be employed for the preparation of an alkene, provided that a mixture of isomers is not produced. The strong bases that are commonly used for these eliminations are sodium hydroxide, potassium hydroxide, sodium methoxide ($NaOCH_3$), and sodium ethoxide ($NaOCH_2CH_3$). Potassium *tert*-butoxide (*t*-BuOK) is especially useful with less hindered substrates to avoid competing substitution. Sulfonate esters can also be used as leaving groups. Several examples are shown in the following reactions:



PROBLEM 10.26

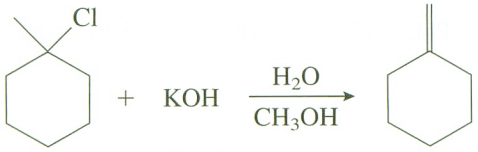
Show the products of these reactions:



PROBLEM 10.27

Explain whether these elimination reactions would be a good way to prepare these alkenes:

a)



b) $PhCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 + NaOEt \xrightarrow{EtOH} PhCH{=}CHCH_3$

PROBLEM 10.28

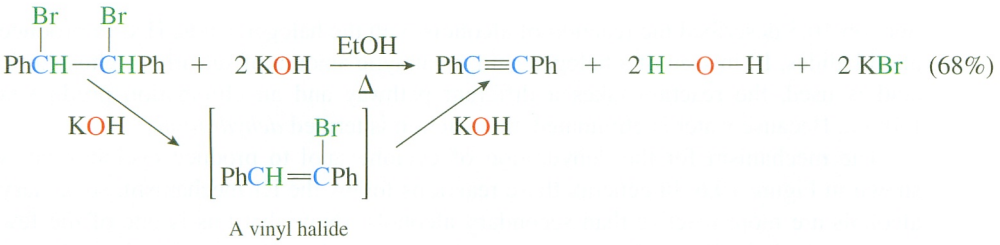
Explain which of these reactions would provide a better synthesis of 2-pentene:

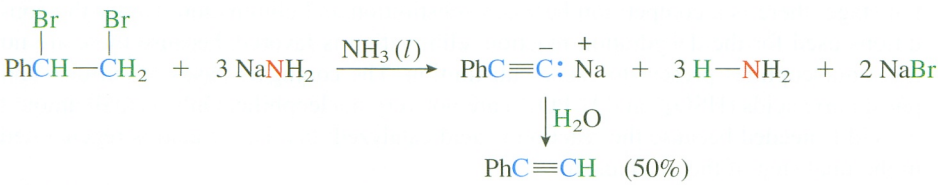
$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 + CH_3O^- \xrightarrow{CH_3OH} CH_3CH{=}CHCH_2CH_3$$

$$CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3 + CH_3O^- \xrightarrow{CH_3OH} CH_3CH{=}CHCH_2CH_3$$

10.12 PREPARATION OF ALKYNES

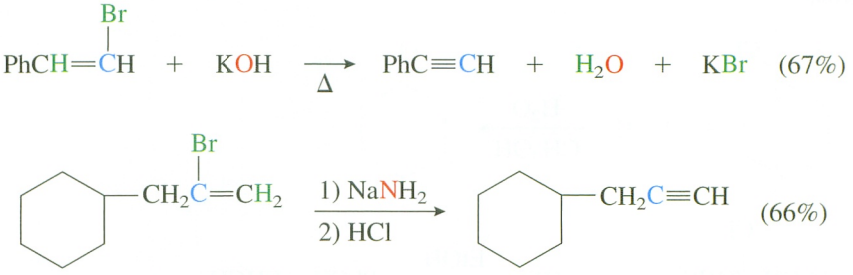
Alkynes can be prepared from dihaloalkanes by elimination of two molecules of HX. This reaction requires very strongly basic conditions so potassium hydroxide at elevated temperatures or the stronger base sodium amide ($NaNH_2$) is commonly employed. Examples are provided by the following equations:





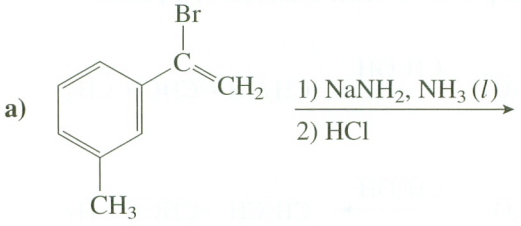
In these reactions, elimination of the first molecule of HX results in the formation of a vinyl halide—an alkene with a halogen bonded to one of the carbons of the double bond. A second, more difficult elimination (this is why the strong base is necessary) pro-

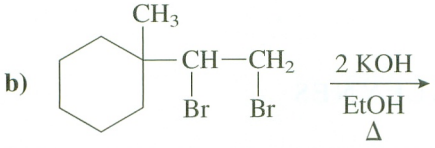
duces the triple bond. Therefore, it is not surprising that vinyl halides can also be used to prepare alkynes, as shown in the following reactions:



PROBLEM 10.29

Show the products of these reactions:





10.13 DEHYDRATION

Section 10.5 described the reaction of alcohols with the halogen acids, HX, to produce alkyl halides. If, instead of a halogen acid, a catalytic amount of sulfuric or phosphoric acid is used, the reaction takes a different pathway and an elimination product is formed. Because water is eliminated, the reaction is termed *dehydration.*

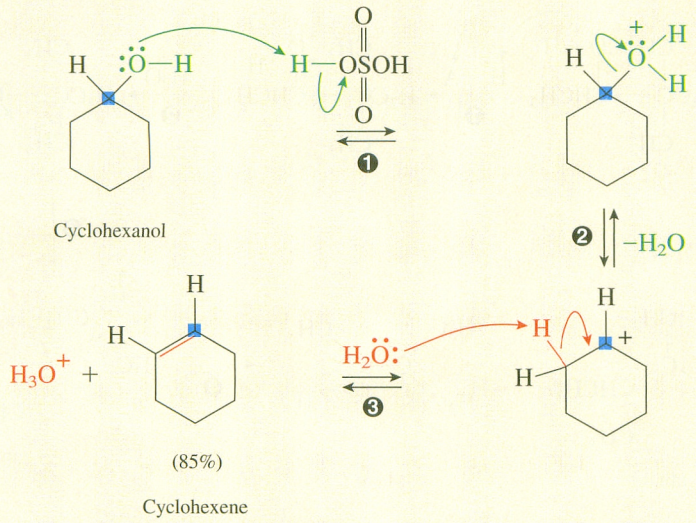
The mechanism for the dehydration of cyclohexanol to produce cyclohexene is shown in Figure 10.6. In general, these reactions follow the E1 mechanism, so tertiary alcohols are more reactive than secondary alcohols. (Note that this is one of the few cases in which the E1 mechanism is favored over the S_N1 mechanism.) At the carbocation stage, there is a competition between substitution and elimination. Under the conditions used for the dehydration reaction, elimination is favored, because there are no good nucleophiles present to cause substitution. The conjugate bases of sulfuric and phosphoric acids (HSO_4^- and $H_2PO_4^-$) are not very nucleophilic. Only a small amount of acid is needed because the reaction is acid catalyzed; that is, the acid is regenerated in the final step of the mechanism.

The dehydration reaction has some limitations. Because the mechanism is E1 and involves a carbocation, rearrangements are possible. Figure 10.7 shows an example of a dehydration involving a carbocation rearrangement. In addition, the reaction is not

ORGANIC Chemistry Now™
Click *Mechanisms in Motion* to view the **Dehydration of Cyclohexanol.**

❶ A proton is transferred from the acid to the oxygen of the alcohol, making a better leaving group.

❷ Water leaves, generating a carbocation. This is the E1 mechanism. Substitution by the competing S_N1 mechanism is avoided because of the absence of good nucleophiles in the reaction mixture. In contrast, if an acid with a nucleophilic conjugate base, such as HCl, were used, substitution products would be formed.

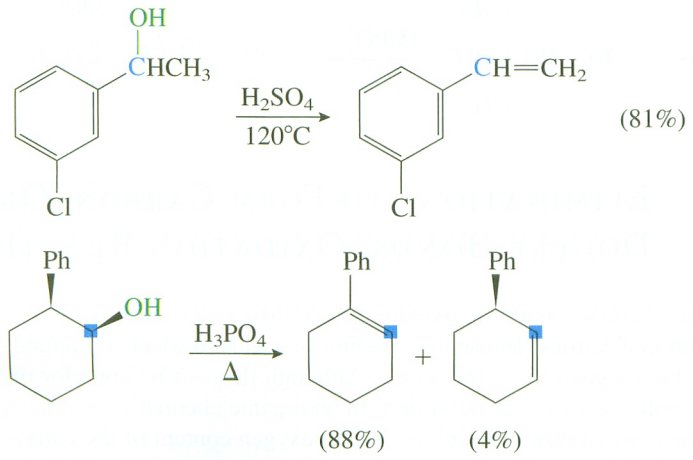


❸ A weak base in the reaction mixture, such as water, removes a proton to produce the alkene. This step regenerates the acid that was used in ❶. Because the acid is not used up, the reaction is catalyzed by acid.

Figure 10.6

MECHANISM OF THE E1 DEHYDRATION OF CYCLOHEXANOL.

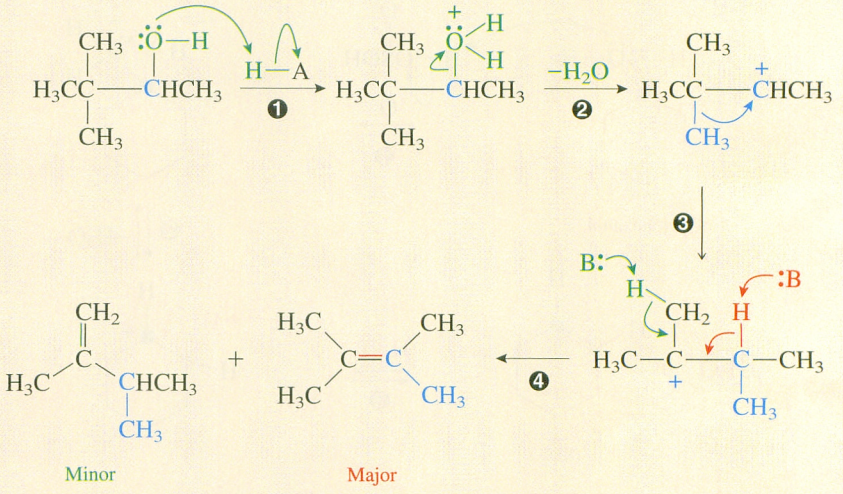
practical when isomeric products can be formed unless there is some factor that causes one product to greatly predominate. As long as these limitations are recognized, the reaction can be useful, as illustrated in the following examples:



❶ The oxygen of the hydroxy group is protonated.

❷ Water leaves, generating a carbocation. Any reaction that involves a carbocation as an intermediate should always be examined for the possibility of rearrangement.

❸ In this case, migration of a methyl group from the adjacent carbon converts the secondary carbocation to a more stable tertiary carbocation.



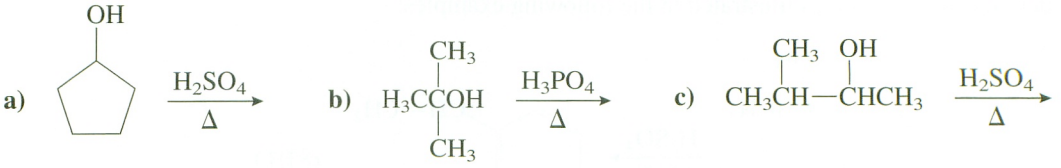
❹ The tertiary carbocation can produce two isomeric alkenes by loss of a proton. Because E1 eliminations follow Zaitsev's rule, the major product is the more highly substituted alkene. Some of the product derived from the unrearranged carbocation may also be formed.

Active Figure 10.7 ORGANIC Chemistry Now™

MECHANISM OF AN E1 DEHYDRATION INVOLVING REARRANGEMENT. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

PROBLEM 10.30

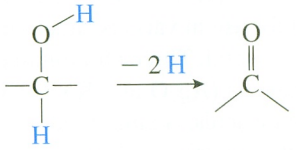
Show the products of these reactions:



10.14 ELIMINATIONS TO FORM CARBON–OXYGEN DOUBLE BONDS; OXIDATION REACTIONS

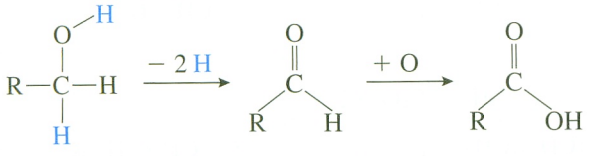
In beginning chemistry courses, oxidation is defined as a loss of electrons and reduction as a gain in electrons. To use these definitions with covalent compounds, oxidation states must be assigned to all the atoms. Although this can be done for organic compounds, we will use a simpler definition. In an organic chemist's vocabulary an **oxidation** is a reaction that results in an increase in oxygen content of the compound and/or a decrease in hydrogen content. Similarly, a **reduction** is a reaction that results in a de-

crease in oxygen content of the compound and/or an increase in hydrogen content. According to these definitions, the conversion of an alcohol to a carbonyl group

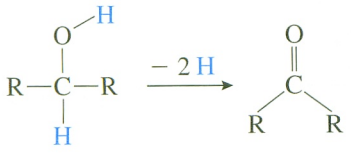


is an example of an oxidation reaction because two hydrogens are lost during the reaction. The reverse of this reaction, the addition of two hydrogens to the carbon–oxygen double bond, is a reduction.

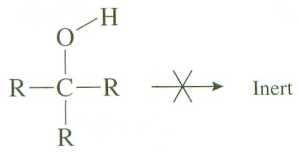
Oxidation of a primary alcohol produces an aldehyde. Further oxidation of an aldehyde to produce a carboxylic acid occurs readily. Therefore, if it is desired to stop the reaction at the aldehyde stage, special reagents must be employed. Secondary alcohols are oxidized to ketones. Tertiary alcohols are inert to most oxidizing reagents.



Primary alcohol — Aldehyde — Carboxylic acid

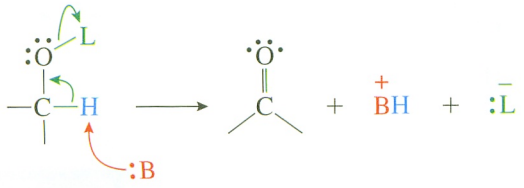


Secondary alcohol — Ketone

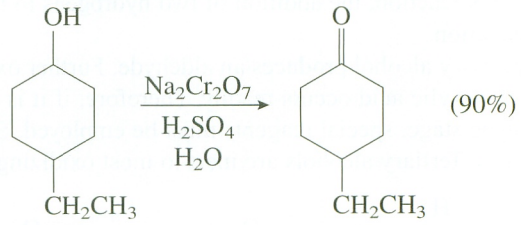


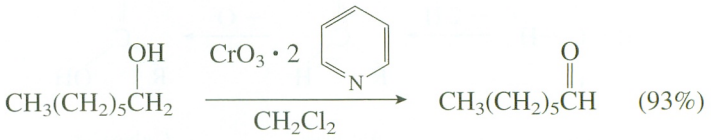
Tertiary alcohol

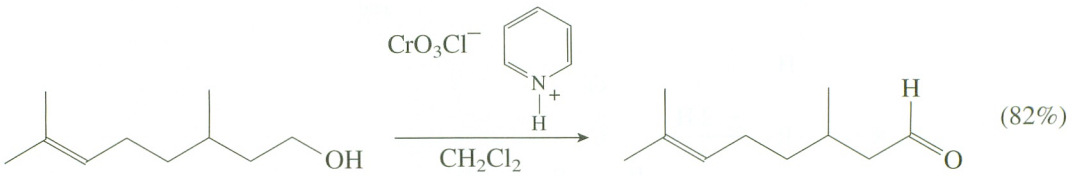
To accomplish the preceding reactions, it is necessary to replace the hydrogen on the oxygen with some group that can act as a leaving group—that is, a group that can leave with the bonding pair of electrons. The following equation shows the similarity of this process to the other eliminations presented in this chapter. The difference here is that the "leaving group" is on an oxygen rather than a carbon.

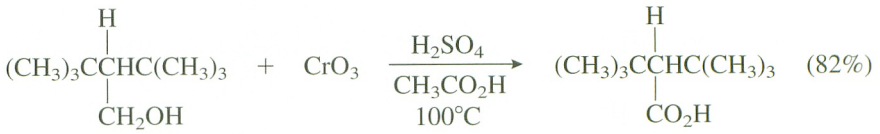


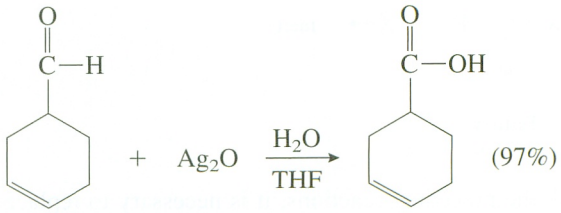
The species that are used as leaving groups in this reaction are most commonly metals in high oxidation states. When the metals leave, taking the electron pair of the metal–oxygen bond with them, they are "reduced." A large number of oxidation reagents have been developed for use in various situations. Ones based on chromium in the +6 oxidation state are very useful. Three chromium oxidation reagents are listed in Table 10.1 along with two reagents (Ag_2O and $KMnO_4$) that are effective for the oxidation of aldehydes to carboxylic acids. A simplified mechanism for the oxidation of 2-propanol to 2-propanone with chromic acid, H_2CrO_4, is illustrated in Figure 10.8. Examples of oxidations using these reagents are shown in the following equations:











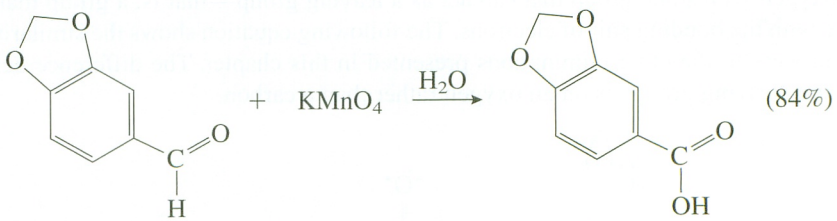
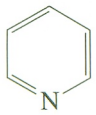
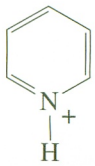
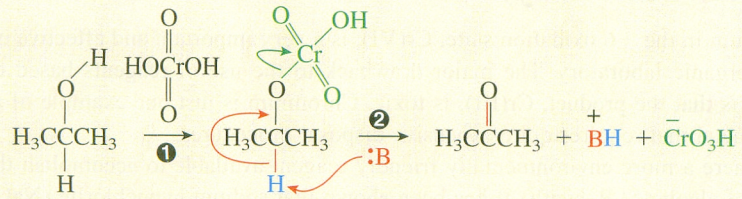


Table 10.1 Some Useful Oxidizing Reagents

Reagent	Comments
$Na_2Cr_2O_7$, $K_2Cr_2O_7$, or CrO_3 in H_2SO_4 and H_2O	Used for simple alcohols that can tolerate acidic conditions; good for oxidizing secondary alcohols to ketones; can be used to oxidize primary alcohols to carboxylic acids.
$CrO_3 \cdot 2$ 	Chromium trioxide–pyridine complex is used when nonacidic conditions are needed; good for converting secondary alcohols to ketones or primary alcohols to aldehydes without overoxidation.
$\overline{C}rO_3Cl$ 	Pyridinium chlorochromate (PCC) is good for sensitive compounds; good for converting secondary alcohols to ketones or primary alcohols to aldehydes without overoxidation.
$KMnO_4$ or Ag_2O	Potassium permanganate and silver oxide are used for oxidation of aldehydes to carboxylic acids.



This is a simplified mechanism for the oxidation of 2-propanol by Cr^{6+}.

❶ The first step involves the reaction of the alcohol with the acid to form a chromate ester. (The mechanism for this step is not important now.)

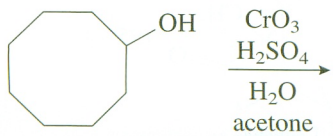
❷ The chromium leaves, taking the bonding electron pair with it. Overall, 2-propanol has been oxidized to acetone, and the chromium has been reduced from the +6 oxidation state in H_2CrO_4 to the +4 oxidation state in H_2CrO_3. The mechanism has additional steps that result in the final oxidation state of the chromium being +3.

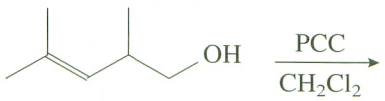
Figure 10.8

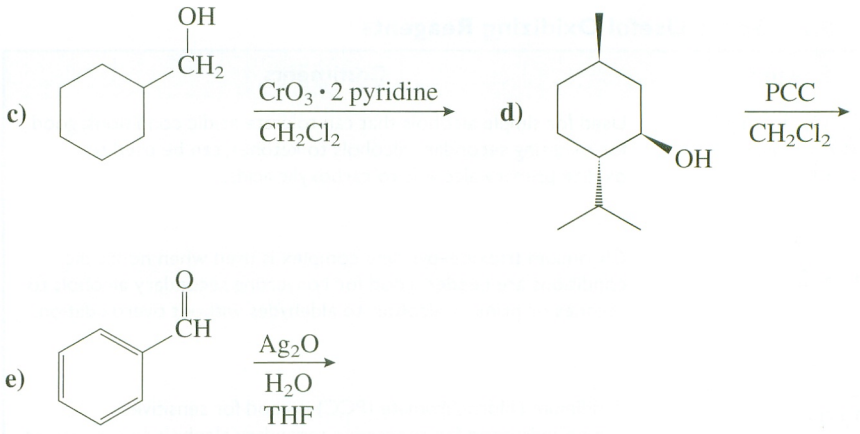
MECHANISM OF THE OXIDATION OF 2-PROPANOL TO 2-PROPANONE.

PROBLEM 10.31

Show the products of these reactions.

a) 

b) 

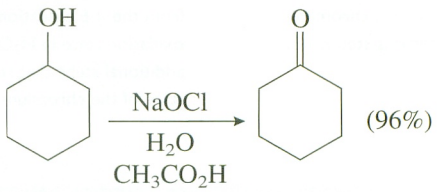


Focus On

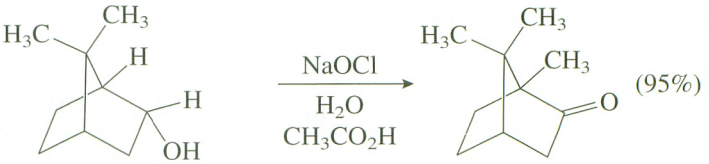
Environmentally Friendly Chemistry (Green Chemistry)

Chromium in the +6 oxidation state, Cr(VI), is a very important and effective oxidant in the organic laboratory. The major drawback to the use of reagents based on this species is that the product, Cr(III), is toxic. Chromium is just one example of a toxic heavy metal that requires quite expensive disposal procedures.

Is there a more environmentally friendly reagent available to accomplish the oxidation of alcohols? Recently, it has been shown that sodium hypochlorite (NaOCl) in acidic solution is an excellent reagent for the oxidation of secondary alcohols to ketones. Examples are shown in the following equations:



Cyclohexanol Cyclohexanone

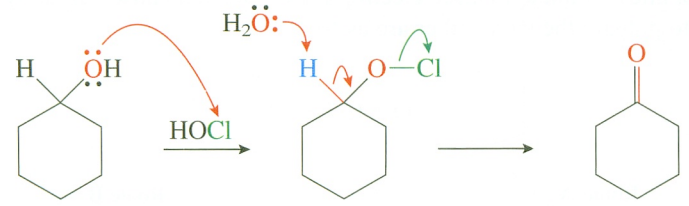


Borneol Camphor

Sodium hypochlorite is an inexpensive, environmentally benign reagent that is available in the form of "swimming pool chlorine," the material that is used to disinfect

swimming pools. An even more convenient source is laundry bleach, a 5.25% solution of sodium hypochlorite that is available in most grocery stores.

The mechanism for this reaction is thought to involve initial chlorination of the hydroxy group to form an alkyl hypochlorite intermediate. An E2 elimination of HCl from this intermediate produces the ketone:



Cyclohexanol An alkyl hypochlorite Cyclohexanone

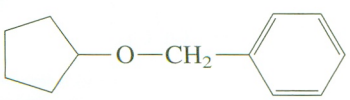
The development of environmentally safe reagents that can be used to replace more toxic materials in organic reactions is an area that deserves and is receiving considerable research attention, especially in industrial laboratories. All chemists need to be conscious of the effect on the environment of each reaction that they run.

10.15 The Strategy of Organic Synthesis

A common problem that an organic chemist faces in the laboratory is the lack of availability of a compound. Perhaps the compound is needed to test as a new pharmaceutical or to test a postulated reaction mechanism. If the compound is not available from a chemical supply house, the chemist is faced with the task of synthesizing it. The first step is to check the chemical literature to determine whether anyone else has ever prepared that compound. If the compound has never been prepared or if the reported preparation is difficult or of low yield, the chemist must design a new synthesis of the compound. How does an organic chemist approach such a problem?

The chemist does not begin by considering how to convert some compound that is available into the desired compound, the **target.** Instead, the question that is asked is "What reaction could I use to make the target compound from a simpler compound?" The simpler compound then becomes the new target compound, and the process is repeated until a commercially available compound is reached. Overall, many steps may be involved in the proposed synthesis. This process of working backward from the target compound is called **retrosynthetic analysis.** Often, several routes to the target compound can be envisioned. The best route depends on a number of factors, such as the number of steps, the yield of each step, and the overall cost. In fact, which route is "best" often depends on why the compound is needed. When a small amount of the compound is needed in a research laboratory, time is often the most important consideration. In contrast, cost is of utmost importance for a compound that is to be prepared on a large scale for commercial purposes.

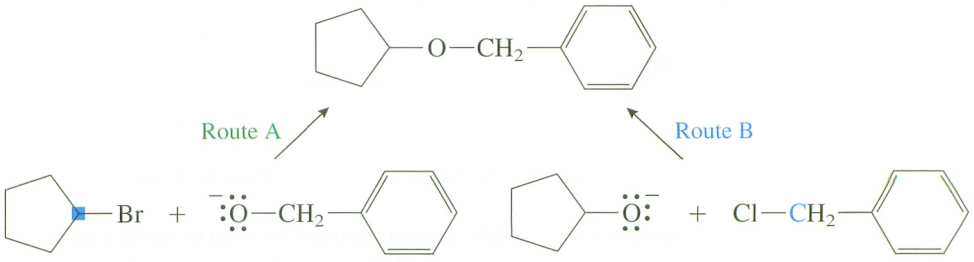
Some examples will help clarify this process. Suppose the target is benzyl cyclopentyl ether:



Benzyl cyclopentyl ether

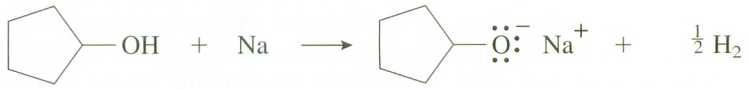
and we are asked to make it starting from alkyl halides. (Because you do not know which compounds can be purchased or are readily available, this book will specify the starting compound for the synthesis in some other fashion, such as here where the type of functional group is designated.)

First, we recall that ethers can be prepared by substitution reactions of alkoxide anion nucleophiles with alkyl halide electrophiles—the Williamson ether synthesis. The two ways to prepare the target ether are as follows:



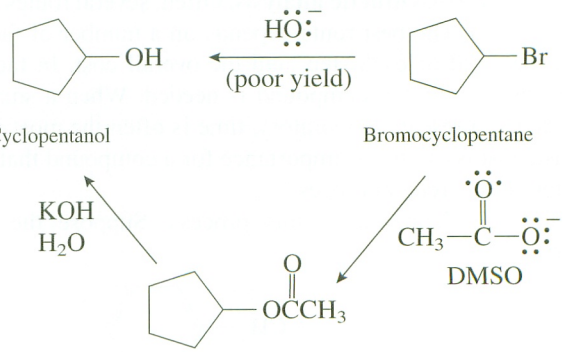
Next, we examine the two reactions to determine whether both are expected to give a good yield of the target compound. Because route A combines a strongly basic nucleophile and a secondary alkyl halide, we expect the major product to result from elimination by the E2 mechanism. Route B, on the other hand, employs a primary alkyl halide that cannot give elimination (it has no hydrogen on the β-carbon) and that is an excellent substrate for an S_N2 substitution because it is benzylic. Route B is the obvious choice.

Benzyl chloride is an acceptable starting material, because the problem has specified that we must start with alkyl halides. However, we must still prepare the alkoxide anion. This is the conjugate base of cyclopentanol and can be made by the reaction of the alcohol with sodium metal:



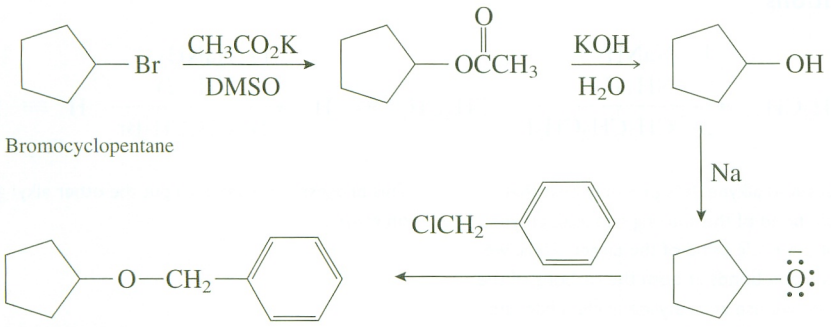
Cyclopentanol

The target is now cyclopentanol. Alcohols can be prepared from alkyl halides by reaction with hydroxide ion as the nucleophile. Again, however, the combination of a strongly basic nucleophile and a secondary alkyl halide will result in an unacceptable amount of elimination. A better plan is to treat bromocyclopentane with acetate ion in an aprotic solvent such as DMSO, followed by cleavage of the ester to cyclopentanol:



Cyclopentanol Bromocyclopentane

Written in the forward direction, our proposed synthesis of benzyl cyclopentyl ether is as follows:



Bromocyclopentane

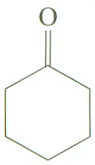
Benzyl cyclopentyl ether

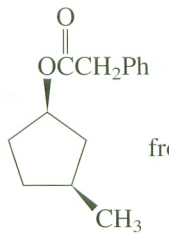
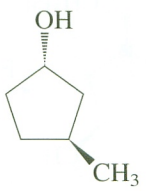
Only a few reactions have been presented so far, so these synthesis problems are fairly easy. But as you learn additional reactions, the syntheses will become longer and more complex, and the value of using retrosynthetic analysis will be more apparent. Because synthesis problems such as this one require a somewhat different thought process than you have been using, they are an excellent way to determine whether you have a good command of the reactions.

PRACTICE PROBLEM 10.3

Show syntheses of these compounds from the indicated starting materials:

a) $CH_3CH_2C{\equiv}CCH_2CH_2CH_3$ from $HC{\equiv}CH$

b)  from an alkyl halide

c)  from 

Strategy

Remember that it helps to use retrosynthetic analysis in synthesis problems. This means working backward to simpler and simpler compounds until an available compound is reached. These problems offer an additional clue in that the starting material is specified. In such cases it is often useful to identify which carbons in the target come from the carbons of the starting material. It is usually advisable to change these carbons as little as possible. It is also useful to identify which carbon–carbon bonds must be formed in the synthesis and how any functional groups need to be modified. In some cases the entire path will be apparent after this examination. In others it will be neces-

sary to proceed backward one step at a time and repeat the examination at each step. Let's try some examples.

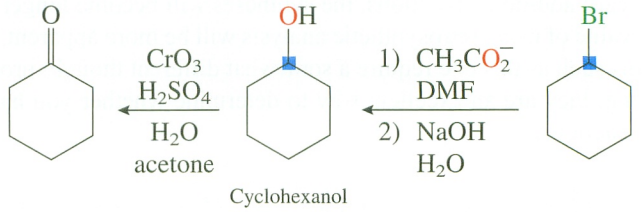
Solutions

a) $CH_3CH_2C{\equiv}CCH_2CH_2CH_3$ ← (1) $NaNH_2$, NH_3 (l); (2) $CH_3CH_2CH_2I$ — $CH_3CH_2C{\equiv}CH$ ← (1) $NaNH_2$, NH_3 (l); (2) CH_3CH_2Br — $HC{\equiv}CH$ (Ethyne)

The initial target is a disubstituted alkyne. It is probably best that the two carbons of the triple bond of the starting material, ethyne, become the two carbons of the triple bond of the target. Thus, we need to form new carbon–carbon bonds at both the carbons of the triple bond. This suggests that we use an acetylide nucleophile and the appropriate alkyl group attached to a halogen leaving group in an S_N2 reaction. The order in which we add the alkyl groups does not make much difference. The reaction is accomplished by treating the 1-alkyne with sodium amide followed by the alkyl halide.

This process is repeated to put the other alkyl group on ethyne.

b)

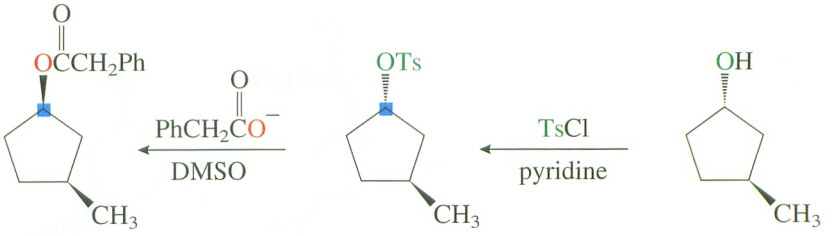


Cyclohexanol

First, note that we do not have to change the carbon skeleton. We merely have to change the functional group from a bromide to a ketone. We do not know how to do this directly, but we do know how to make a ketone by the oxidation of a secondary alcohol.

The target is now cyclohexanol, a secondary alcohol. The reaction of a secondary alkyl halide with hydroxide ion gives an unacceptably high amount of elimination by the E2 mechanism. A better choice is to use acetate ion as the synthetic equivalent of hydroxide ion.

c)



Comparison of the target to the starting material shows that we need to substitute the ester group for the hydroxy group with inversion of configuration. So we need to convert the OH to a leaving group and do an S_N2 reaction. We can convert the OH to a tosylate or mesylate ester. Then do an S_N2 substitution using the carboxylate anion as the nucleophile in an aprotic solvent such as DMSO.

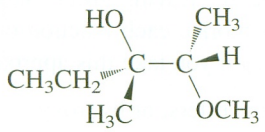
PROBLEM 10.32

Show syntheses of these compounds from the indicated starting materials.

a) $CH_3CH_2CH_2CH_2\overset{+}{N}(CH_3)_3\ I^-$ from compounds with none of the CN bonds of the final product

b) $CH_3CH_2O\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$ from alkyl halides

c) from

d)  from an epoxide

e) $PhCH_2C{\equiv}CCH_3$ from $HC{\equiv}CH$

Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the major product(s) of any of the reactions discussed in this chapter. (Problems 10.33, 10.36, and 10.40)
- Show the stereochemistry of the product(s). (Problems 10.33, 10.43, 10.55, 10.56, 10.57, 10.58, and 10.59)
- Write the mechanisms of these reactions. (Problems 10.42, 10.44, 10.46, 10.50, 10.51, 10.52, and 10.53)
- Synthesize compounds using these reactions. (Problems 10.34, 10.35, 10.37, 10.38, 10.39, 10.41, 10.47, and 10.54)

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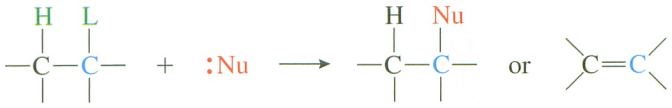
Click *Mastery Goal Quiz* to test how well you have met these goals.

Visual Summary of Key Reactions

This chapter has presented a large number of reactions. Yet most of them fall into one of two classes. A nucleophile or base reacts with a substrate containing a leaving group in either a substitution reaction, in which the nucleophile replaces the leaving group on the electrophilic carbon, or an elimination reaction, in which a double bond is formed between the electrophilic carbon and an adjacent carbon:



It is very important to be able to recognize the nucleophile, the leaving group, and the electrophilic carbon. So, rather than just attempting to memorize each reaction on its own, you will have more success in learning these reactions if you take this approach:

1. Identify the leaving group (halides, sulfonate and related esters, or hydroxy groups under acidic conditions).
2. Identify the electrophilic carbon (the one bonded to the leaving group).
3. Identify the base or nucleophile (has an atom with an unshared pair of electrons).
4. Identify the mechanism by which the reaction proceeds (S_N1, S_N2, E1, or E2).
5. For substitutions, replace the leaving group with the nucleophile with inversion for S_N2 and racemization for S_N1.
6. For eliminations, form the carbon–carbon double bond according to Zaitsev's rule (except the Hofmann elimination) and use anti elimination to determine the stereochemistry of E2 reactions.
7. Consider the possibility of carbocation rearrangements for all S_N1 and E1 reactions.

The substitution reactions covered in this chapter are summarized in Table 10.2, and the elimination reactions are summarized in Table 10.3.

Table 10.2 Summary of Substitution Reactions

Reaction	Comments
Section 10.2 Preparation of Alcohols	
$R{-}X + {}^{-}\!:\!\ddot{O}{-}H \longrightarrow R{-}OH$	S_N2 conditions; strong base, so secondary substrates give significant elimination
$R{-}X + H_2O \longrightarrow R{-}OH$	S_N1 conditions (unless primary); hydrolysis (solvolysis)
$R{-}X \xrightarrow[2)\ KOH,\ H_2O]{1)\ CH_3CO_2^-} R{-}OH$	S_N2 conditions; weak base, so fewer elimination problems with secondary substrates; synthetic equivalent of hydroxide ion
Section 10.3 Preparation of Ethers	
$R{-}L + {}^{-}\!:\!\ddot{O}{-}R' \longrightarrow R{-}O{-}R'$	S_N2 conditions; Williamson ether synthesis; strong base, so secondary substrates give mostly elimination; often two routes to same product
$ROH + Na \longrightarrow R{-}\ddot{O}\!:^{-}\ Na^{+}$	Preparation of alkoxide nucleophile and base
$PhOH + K_2CO_3 \longrightarrow Ph{-}\ddot{O}\!:^{-}\ K^{+}$	Preparation of phenoxide nucleophile
$R{-}L + HOR' \longrightarrow R{-}O{-}R'$	S_N1 conditions (unless primary); solvolysis
Section 10.4 Preparation of Esters	
$R{-}L + {}^{-}\!:\!\ddot{O}{-}\overset{\overset{O}{\|}}{C}R' \longrightarrow R{-}\ddot{O}{-}\overset{\overset{O}{\|}}{C}R'$	S_N2 conditions; weak base, so good yields with secondary substrates
Section 10.5 Preparation of Alkyl Halides	
$R{-}OH + \begin{matrix}HCl\\ \text{or}\\ HBr\\ \text{or}\\ HI\end{matrix} \longrightarrow \begin{matrix}R{-}Cl\\ \text{or}\\ R{-}Br\\ \text{or}\\ R{-}I\end{matrix}$	S_N1 conditions (unless primary); watch for rearrangements; HCl requires $ZnCl_2$ for primary and secondary alcohols
$R{-}OH \xrightarrow[2)\ :\!\ddot{X}\!:^{-}]{1)\ TsCl} R{-}X$	S_N2 conditions
$R{-}OH + \begin{matrix}SOCl_2\\ \text{or}\\ PBr_3\\ \text{or}\\ PI_3\end{matrix} \longrightarrow \begin{matrix}R{-}Cl\\ \text{or}\\ R{-}Br\\ \text{or}\\ R{-}I\end{matrix}$	S_N1 or S_N2; thionyl chloride, phosphorus tribromide, and phosphorus triiodide provide a good one-step procedure for conversion of an alcohol to an alkyl chloride, bromide, or iodide
$R{-}\ddot{X}\!: + :\!\ddot{X}\!:^{-} \longrightarrow R{-}\ddot{X}\!: + :\!\ddot{X}\!:^{-}$	S_N2 conditions; must drive equilibrium

Continued

Table 10.2 Summary of Substitution Reactions—cont'd

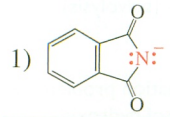
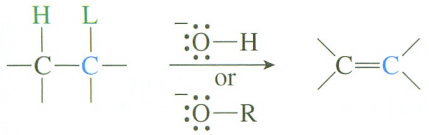
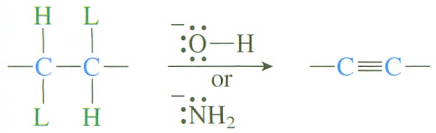
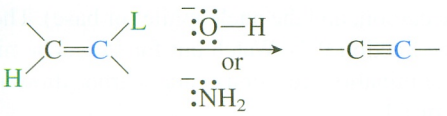
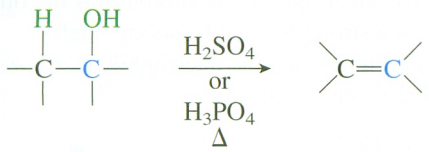
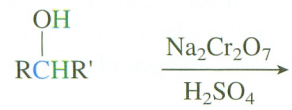
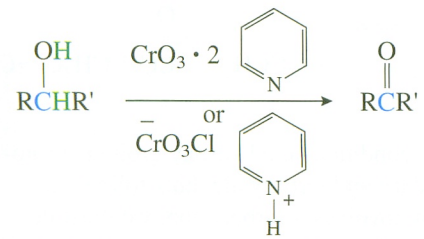
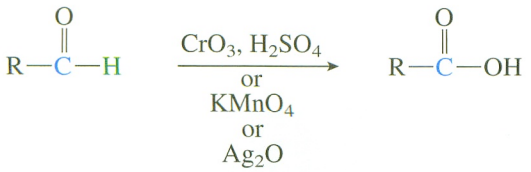
Reaction	Comments
Section 10.6 Preparation of Amines	
$R{-}L + \ddot{N}H_3 \longrightarrow R{-}\overset{+}{N}H_3$	S_N2 conditions; problem with multiple alkylation; acceptable yields for tertiary amines and quaternary ammonium salts
$R{-}L \xrightarrow[2)\ KOH,\ H_2O]{1)\ \text{  }} R{-}NH_2$	S_N2 conditions; Gabriel synthesis; synthetic equivalent of ammonia; yields acceptable with secondary substrates
Section 10.7 Preparation of Hydrocarbons	
$R{-}L \xrightarrow{LiAlH_4 \text{ or } NaBH_4} R{-}H$	S_N2 conditions; lithium aluminum hydride and sodium borohydride give acceptable yields with primary and secondary substrates
Section 10.8 Formation of Carbon–Carbon Bonds	
$R{-}L + {:}\bar{C}{\equiv}N{:} \longrightarrow R{-}C{\equiv}N$	S_N2 conditions; cyanide ion is a weak base, so yields are acceptable with secondary substrates
$R{-}L + {:}\bar{C}{\equiv}C{-}R' \longrightarrow R{-}C{\equiv}C{-}R'$	S_N2 conditions; acetylide anion is a strong base, so yields are satisfactory with primary substrates only
$H{-}C{\equiv}C{-}R' + \bar{:}\ddot{N}H_2 \longrightarrow {:}\bar{C}{\equiv}C{-}R'$	Amide anion is commonly used as the base to prepare acetylide anions
Section 10.9 Phosphorus and Sulfur Nucleophiles	
$R{-}L + \bar{:}\ddot{S}{-}H \longrightarrow R{-}S{-}H$ (or) $\bar{:}\ddot{S}{-}R' \longrightarrow R{-}S{-}R'$	S_N2 conditions; sulfides are weak bases but good nucleophiles; good yields with primary and secondary substrates
$R{-}L + {:}PPh_3 \longrightarrow R{-}\overset{+}{P}Ph_3$	S_N2 conditions; phosphines are weak bases but good nucleophiles; good yields with primary and secondary substrates
Section 10.10 Ring Opening of Epoxides	
	In base, nucleophile bonds to less hindered carbon with inversion (S_N2); in acid, nucleophile bonds to more substituted carbon with inversion (borderline mechanism)

Table 10.3 Summary of Elimination Reactions

Reaction	Comments
Section 10.11 Elimination of Hydrogen Halide (Dehydrohalogenation)	
	E2 conditions; anti elimination and Zaitsev's rule; steric hindrance in either base or substrate slows competing S_N2 reaction
Section 10.12 Preparation of Alkynes	
	E2 conditions
	E2 conditions; vinyl halides are intermediates in the preceding reaction
Section 10.13 Dehydration	
	E1 conditions; dehydration; Zaitsev's rule; rate depends on carbocation stability; watch for rearrangement
Section 10.14 Eliminations to Form Carbon–Oxygen Double Bonds; Oxidation Reactions	
	Good for converting secondary alcohols to ketones and primary alcohols to carboxylic acids; can use $K_2Cr_2O_7$ or CrO_3 also
	Both of these reagents work well for preparation of aldehydes from primary alcohols also
	Chromium (VI), permanganate ion, or silver oxide can all be used to oxidize an aldehyde to a carboxylic acid; Cr^{6+} also oxidizes primary alcohols to carboxylic acids

Integrated Practice Problem

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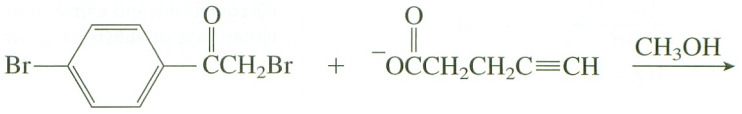
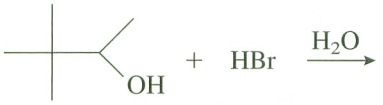
Click *Coached Tutorial Problems* for more practice with **Substitution and Elimination Reactions.**

Show the products of these reactions.

a)

b) 

c) 

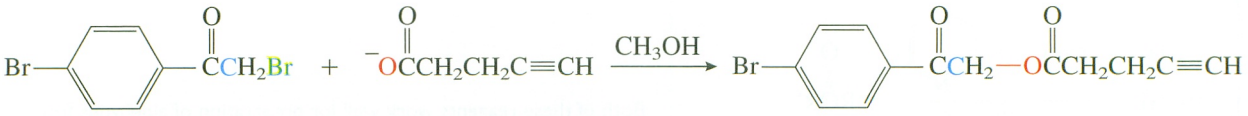
Strategy

Follow the steps listed in the preceding Visual Summary of Key Reactions section. Identify the leaving group, the electrophilic carbon, and the nucleophile (or base). Then determine which mechanism is favored (see Section 9.7). Watch out for stereochemistry where important, regiochemistry in elimination reactions, and carbocation rearrangements when the mechanism is S_N1 or E1.

Solutions

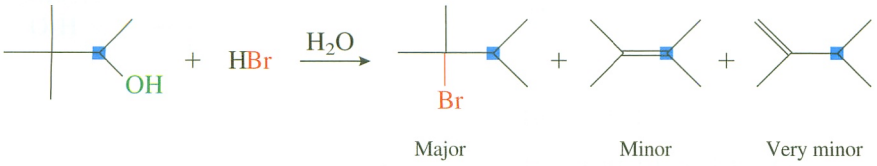
a) The leaving group is the tosylate group. The electrophilic carbon (blue) is the one bonded to the OTs group. Methoxide ion is a strong base and a strong nucleophile. Because the electrophilic carbon is primary and the nucleophile is not sterically hindered, the reaction follows an S_N2 mechanism:

b) There are two bromines in the reactant. However, the one bonded to the benzene ring is inert to substitution and elimination reactions. The other is especially reactive in the S_N2 reaction because it is on a primary carbon (the electrophile) that is adjacent to a carbonyl group. The nucleophile is the negative oxygen of the carboxylate anion:



c) In the reaction of an alcohol under acidic conditions the hydroxy group is protonated and acts as a leaving group. Secondary and tertiary alcohols follow the S_N1/E1 mechanisms. Because the reaction involves a carbocation, we must be aware of the possibility of a rearrangement. In this case, rearrangement does oc-

cur, converting the original secondary carbocation to a more stable tertiary carbocation. Because bromide ion is a good nucleophile, the major product results from substitution. Some elimination product is also formed.



Additional Problems

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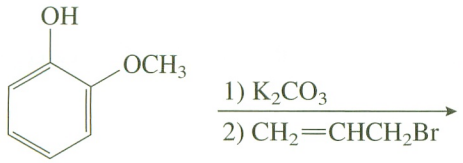
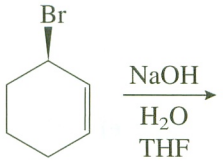
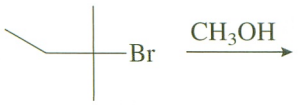
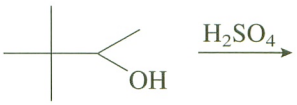
Assess your understanding of this chapter's topics with additional quizzing and conceptual-based problems at **http://now.brookscole.com/hornback2**

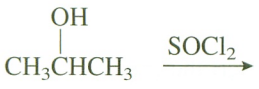
10.33 Show the products of these reactions:

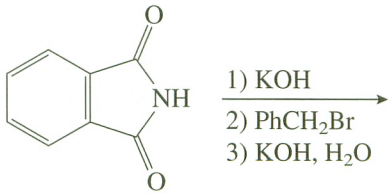
a) 

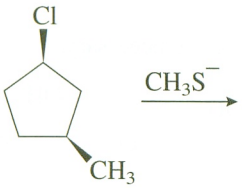
b) 

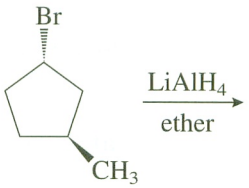
c) 

d) 

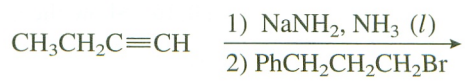
e) 

f) 

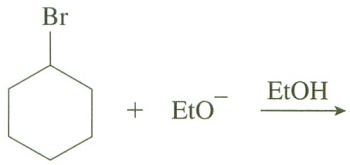
g) 

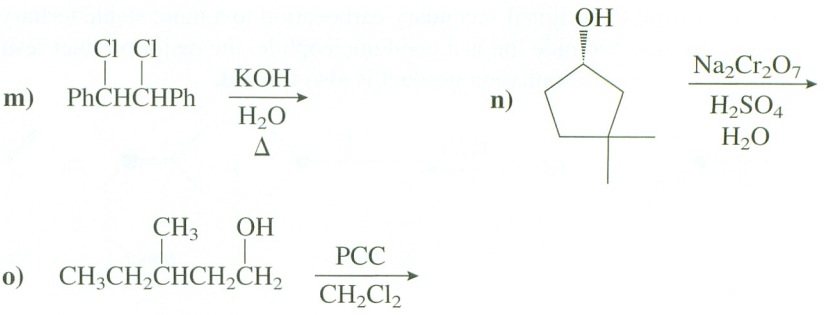
h) 

i)

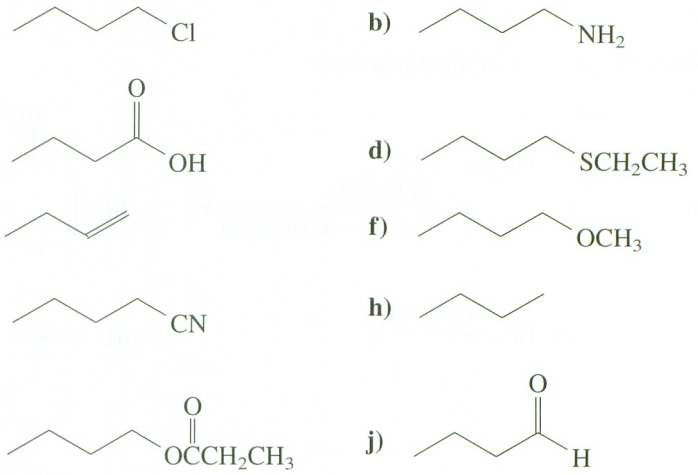
j) 

k)

l) 

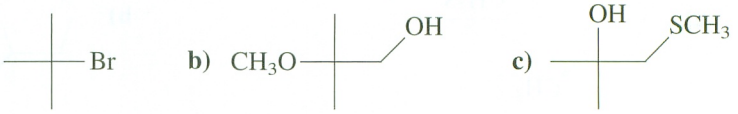


10.34 Show reactions that could be used to convert 1-butanol to these compounds:

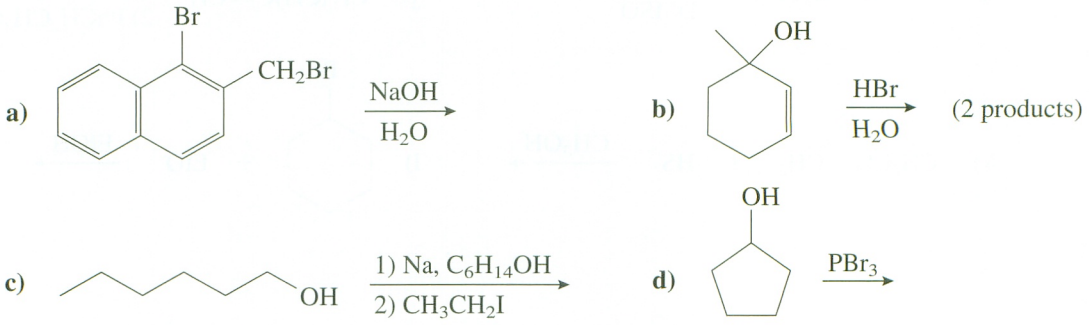


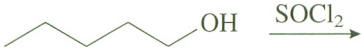
10.35 Show reactions that could be used to convert the epoxide

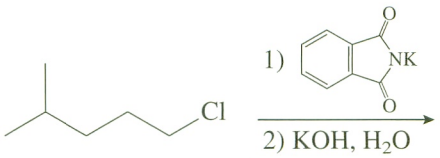
to these compounds. More than one step may be necessary.



10.36 Show the products of these reactions:

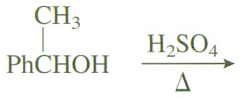


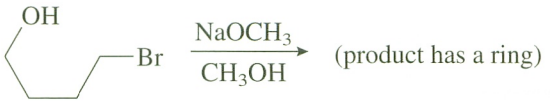
e) 

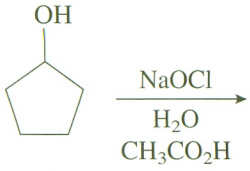
f) 

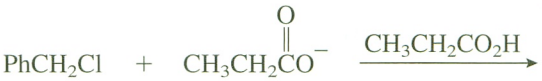
g) $Ph_3P + CH_3CH_2Br \xrightarrow{\text{benzene}}$

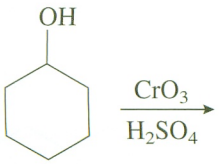
h)

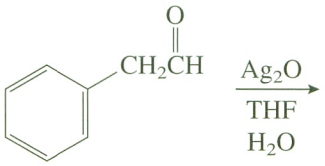
i) 

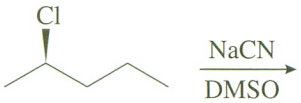
j) 

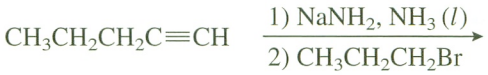
k) 

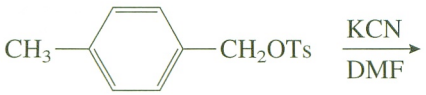
l) 

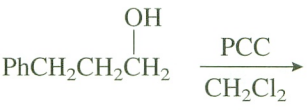
m) 

n) 

o) 

p) 

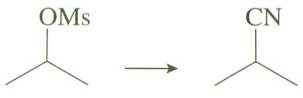
q) 

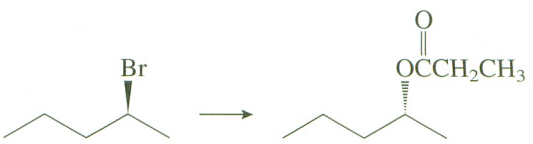
r) 

10.37 Suggest reagents that could be used to accomplish the following transformations.

a)

b)

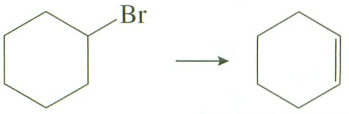
c) 

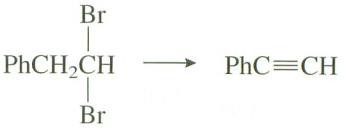
d) 

e)

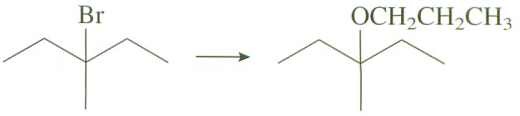
f)

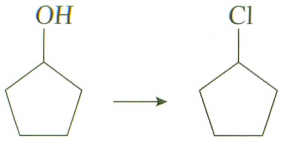
g)

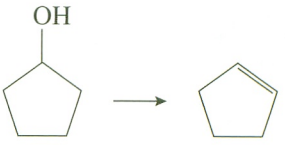
h) 

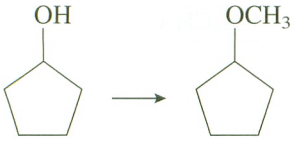
i) 

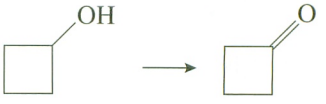
j) $CH_3CH_2Cl \longrightarrow CH_3CH_2OCH_3$

k) 

l) 

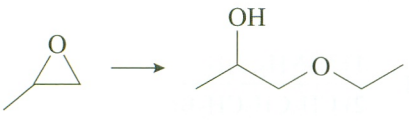
m) 

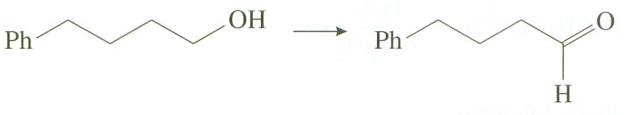
n) 

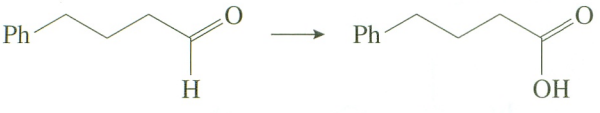
o) 

p)

q)

r) 

s) 

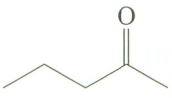
t) 

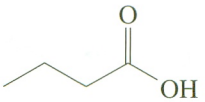
10.38 Show how these compounds could be synthesized from alkyl halides:

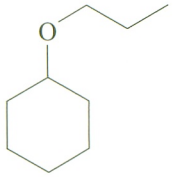
a) Heptane

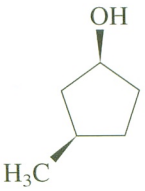
b) $PhCH_2CH_2CH_2NH_2$

c) $PhCH_2C{\equiv}CH$

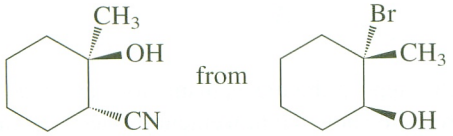
d) 

e) 

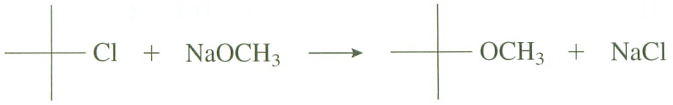
f) 

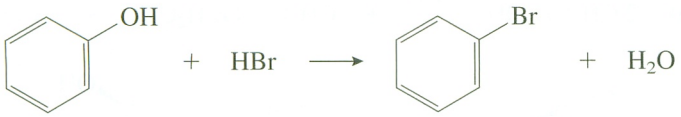
g) 

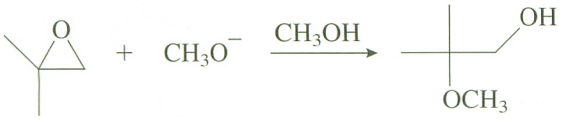
10.39 Show how this synthesis might be accomplished:



10.40 What is wrong with these reactions? Explain.

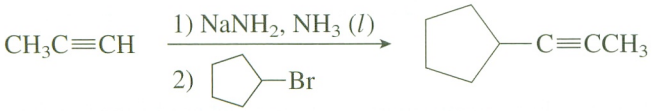
a) 

b) 

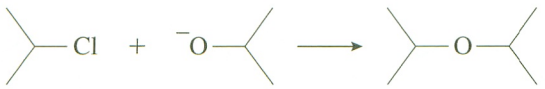
c) 

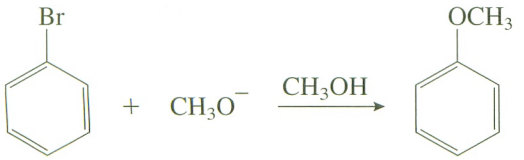
d)

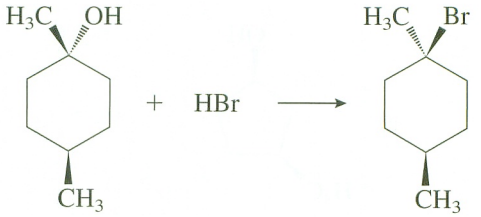
10.41 What is wrong with these syntheses? Explain.

a) 

b)

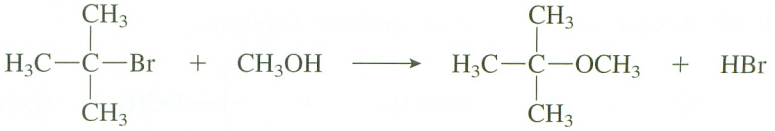
c) 

d) 

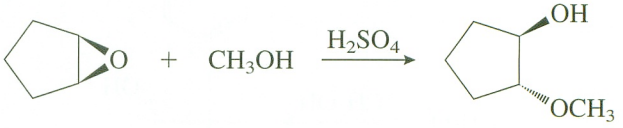
e) 

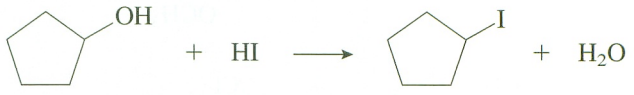
f)

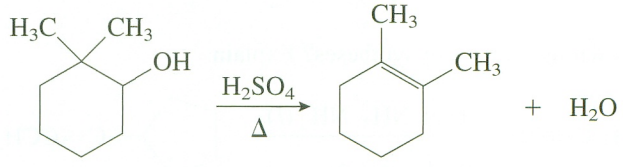
10.42 Show all the steps in the mechanisms for these reactions. Don't forget to use curved arrows to show the movement of electrons in each step.

a) 

b)

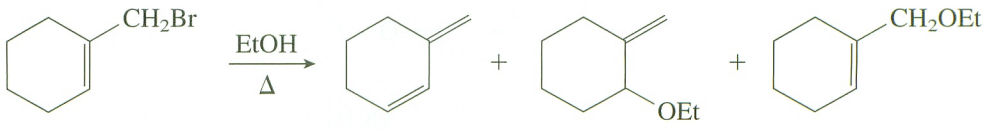
c) 

d) 

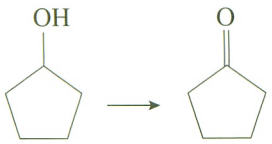
e) 

10.43 Explain how both enantiomers of the product are formed in the reaction shown in problem 10.42c.

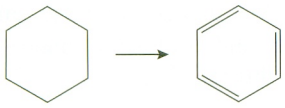
10.44 Show all the steps in the mechanism for this reaction:



10.45 Classify these transformations as oxidations or reductions:

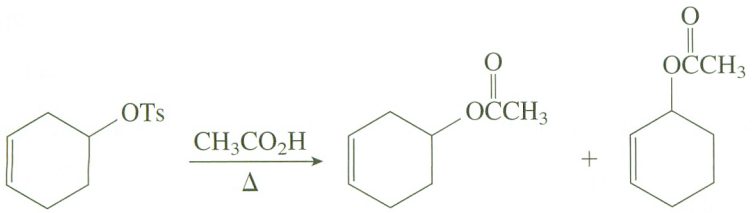
a) 

b)

c) 

d) $CH_3CH_2\overset{O}{\overset{\|}{C}}OH \longrightarrow CH_3CH_2CH_2OH$

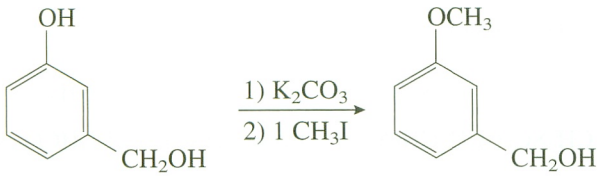
10.46 Show a mechanism for this reaction:



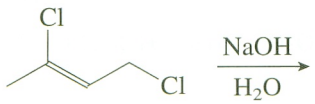
10.47 Show how mustard gas could be prepared from ethylene oxide and sodium sulfide (Na_2S).

Ethylene oxide

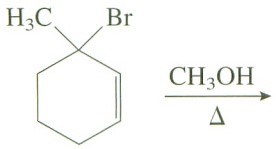
10.48 Explain why one of the oxygens preferentially acts as the nucleophile in this reaction:



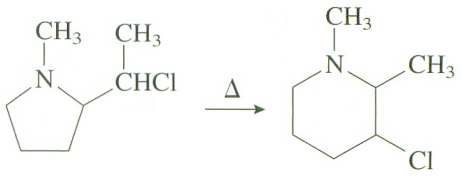
10.49 Only one of the chlorines acts as a leaving group in this reaction. Explain.



10.50 This reaction gives two substitution products. Show the structures for these products and provide a mechanism for their formation.



10.51 Suggest a mechanism for this reaction:



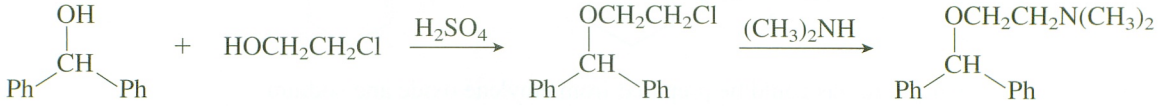
BioLink

10.52 In addition to the reaction shown on p. 353, diphenhydramine can also be prepared by heating bromodiphenylmethane and 2-(dimethylamino)-1-ethanol in a polar solvent. Show a mechanism for this reaction:

Diphenhydramine

BioLink

10.53 Another diphenhydramine synthesis is shown in the following equation:



Diphenhydramine

a) Show a mechanism for the first step in this synthesis.
b) Explain which mechanism is occurring in the second step.

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10.54 Suggest syntheses of these amino acids from the indicated starting materials:

Phenylalanine

Methionine Homocysteine

Cysteine Serine

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10.55 **a)** Explain which of the following two products is formed when the reactant alkyl chloride reacts with sodium acetate in DMSO.
b) Explain which of the following two product alcohols is formed when the product from part a reacts with sodium hydroxide in water.

10.56 Explain which of the following two ether products is formed when the reactant alcohol reacts with sodium followed by reaction with iodomethane.

10.57 Explain which of the following chlorohydrins forms an epoxide more readily upon treatment with base.

10.58 Explain which of the following epoxide products is formed when the chlorohydrin reactant is treated with base.

10.59 **a)** Explain which of the following products is formed when the epoxide reactant is treated with methoxide ion in methanol.
b) Explain which of the products from part a is formed when the epoxide reactant from part a is treated with acid in methanol.

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